The Development of Pd(II)-Catalysed Oxidative Heck Reactions and C-H Functionalisations

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ABSTRACT

This thesis outlines the work undertaken on three projects focusing on the development of Pd(II)-catalysed oxidative Heck reactions and C-H functionalisations.

Chapter one reviews literature related to palladium catalysis, specifically the oxidative Heck reaction, its development and the most recent advances in this area.

Chapter two describes methodology developed to switch the outcome of the ligand- and base-free Pd(II)-catalysed reaction between cyclic enones and boronic acids from conjugate addition to oxidative Heck product, by simply changing the solvent. Additionally, factors which favour one reaction over the other are also discussed.

Chapter three outlines the successful development of a palladium-catalysed direct C-H functionalisation of benzoquinone. Both mono and difunctionalisations can be carried out selectively in excellent yields and a wide variety of functional groups are tolerated. Regioselectivity of the difunctionalisation reactions appears to be determined by the electronic properties of the boronic acid used. A successful one-pot procedure for the heterodifunctionalisation of benzoquinone is also outlined.

Chapter four details the development of oxidative Heck reactions on challenging 2,2-disubstituted cyclopentene-1,3-dione substrates with aryl boronic acids. An efficient enantioselective protocol provides a facile way to desymmetrise the all carbon quaternary stereocentre present in the cyclopentenedione substrates and includes the synthesis of (+)-preussidone.

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ABBREVIATIONS

acac	acetylacetonate
APCI	atmospheric-pressure chemical ionisation
ar	aryl group
(*R*)-BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
(*R*)-MeOBIPHEP	(*R*)-(+)-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Box	bis(oxazoline)
BQ	1,4-benzoquinone
br	broad
°C	degrees Celsius
Cbz	carboxybenzyl
cod	1,5-cyclooctadiene
conv.	conversion
d	doublet
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCBQ	2,6-dichloro-1,4-benzoquinone
DCE	1,2-dichloroethane
DFT	density functional theory
DMA	*N*,*N*-dimethyl acetamide
DMF	*N*,*N*-dimethyl formamide
dmphen	2,9-dimethyl-1,10-phenanthroline
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
er	enantiomeric ratio
equiv.	equivalent

Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
h	hours
Hz	Hertz
HetAr	heteroaromatic
HRMS	high resolution mass spectrometry
I^iPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infra-red
J	coupling constant
m	multiplet
M	molar
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
MHz	Megahertz
min	minutes
mM	millimolar
mmol	millimole
M. p.	melting point
NHC	*N*-heterocyclic carbene
NMM	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
NSI	nano-electrospray ionization
NY	no yield
ND	not determined
OAc	acetate
OTf	trifluoromethanesulfonate
OTs	*p*-toluenesulfonate
Ph	phenyl
phen	1,10-phenanthroline
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl

PyOx	pyridinooxazoline
q	quartet
quant.	quantitative
R	alkyl/aryl group
R_f	retention factor
RMM	relative molecular mass
rt	room temperature
s	singlet
(*S*,*S*)-chiraphos	(2*S*,3*S*)-(−)-Bis(diphenylphosphino)butane
str	strong
t	triplet
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
temp.	temperature
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid (triflic acid)
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultra violet
v str	very strong
w	weak

Chapter 1: Introduction

1.1 Palladium catalysis

The synthesis of C-C bonds has long been a challenge for organic chemists. In the latter part of the 20th century palladium catalysis emerged as an important route to the formation of such bonds.[1-3] Since then, palladium has become one of the most important, versatile and widely-used transition metals in organic synthesis.[1]

The importance of this element, first isolated in 1802 by Wollaston,[4] and its wide application in synthetic chemistry was reflected in the awarding of the 2010 Nobel Prize to Richard Heck, Ei-ichi Negishi and Akira Suzuki for their work on palladium(0)-catalysed cross-coupling reactions.[5] The advances made by their work have revolutionised the way in which molecules are constructed and have provided methods for accessing challenging C-C bond forming processes.

Since the early work by Heck,[6] Negishi[7, 8] and Suzuki,[9] the use of palladium(0) as a catalyst has grown exponentially and a multitude of C-C bond forming reactions are available to organic chemists. Following on from the aforementioned work, additional coupling reactions pioneered by Stille,[10] Sonogashira[11] and Hiyama[12] amongst others have come to the fore and within the last decade, the number of publications and patents featuring named metal-catalysed cross-coupling reactions has grown exponentially.[5, 13]

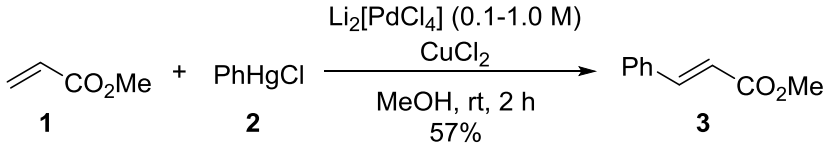
In the early 1970s both Heck[14] and Mizoroki[15] published work independently on the reaction of an unsaturated halide with an alkene in the presence of base and a palladium(0) catalyst. This would later be known as the Mizoroki-Heck reaction. It differs from the other aforementioned Pd(0)-catalysed cross-coupling reactions in that a halide is coupled to an alkene without the need for prefunctionalisation of the latter substrate which is obviously advantageous when compared with other cross-coupling methods.

Following the seminal work of Mizoroki and Heck, further developments of the Heck reaction took place over subsequent decades including the discovery of the Heck-Matsuda reaction whereby aryl diazonium salts rather than an aryl halide are employed as a coupling partner.[16, 17] Numerous developments of the Heck reaction have taken place in the decades since the initial work was reported.[18]

1.2 The oxidative Heck reaction

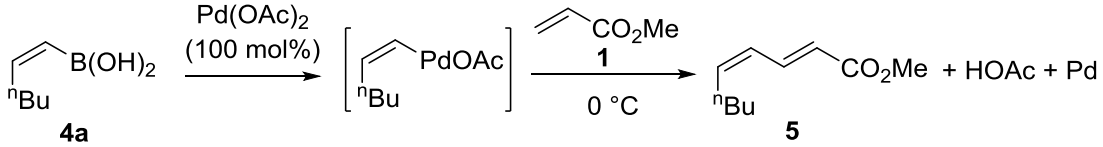
1.2.1 Introduction

Prior to work published on the coupling of an aryl or vinyl halide to an alkene,[14] Heck demonstrated that oxidative coupling of methyl acrylate **1** and phenyl mercuric chloride **2** could be achieved at room temperature using $Li_2[PdCl_4]$ as a catalyst and copper(II) chloride as oxidant to regenerate palladium(II) from palladium(0) (Scheme 1).[6] Heck published seven consecutive publications relating to this work[6, 19-24] but due to the toxicity of organomercurials, alternative methodologies were sought and hence work focussed on the use of aryl halides as coupling partners which became known as the Mizoroki-Heck reaction.



Scheme 1: Oxidative coupling of phenylmercuric chloride and methyl acrylate

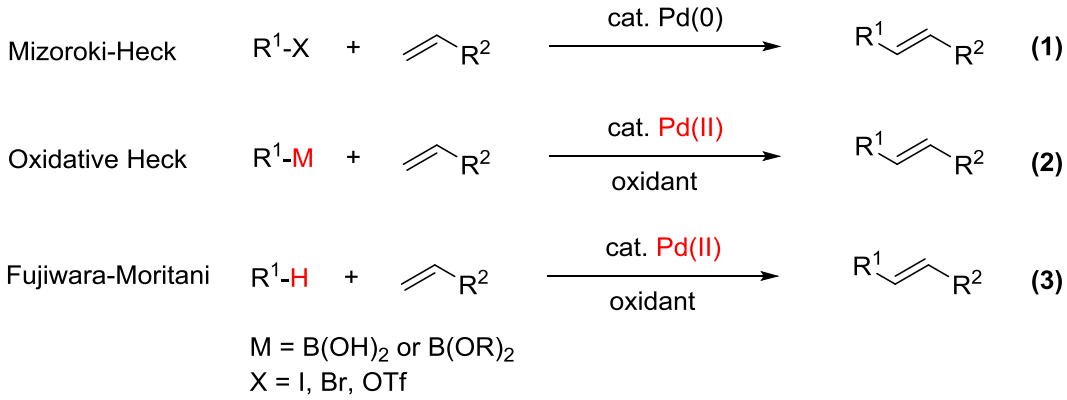
In 1975, in a paper reporting developments in the Pd(0)-catalysed Heck reaction to synthesise conjugated dienes **5**, Dieck and Heck also reported the first Pd(II)-mediated *oxidative* Heck reaction using an organoborane substrate **4a** and stoichiometric amounts of palladium(II) acetate (Scheme 2).[25]



Scheme 2: First Pd(II)-mediated oxidative Heck reaction with organoborane reagents

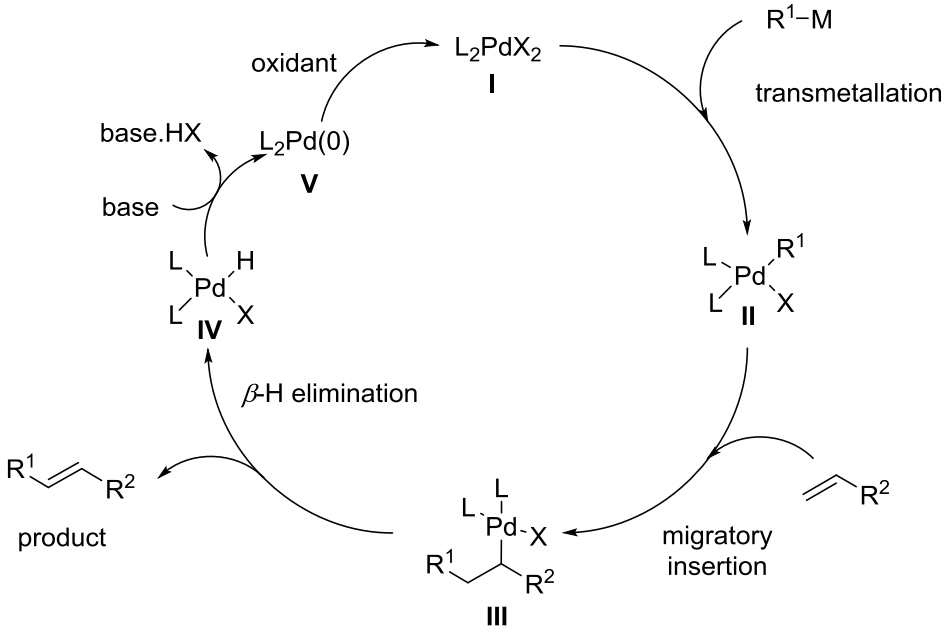
Despite this early work indicating the potential of using Pd(II) rather than Pd(0) for cross-coupling reactions, it was not until a catalytic protocol was developed in 1994 by Cho and Uemura[26] that the oxidative Heck reaction received more attention and became a growing tool for organic synthesis. Formally, the oxidative Heck reaction couples an alkene with an organoboron compound using a Pd(II) catalyst (Scheme 3, Equation 2).

An additional related Pd(II)-coupling is the Fujiwara-Moritani reaction. First reported in 1967 the reaction couples an arene with an alkene by way of CH activation (Scheme 3, Equation 3).[27, 28] This has also gained prevalence in recent years.[29-31]



Scheme 3: Differences between the Mizoroki-Heck, Fujiwara-Moritani and oxidative Heck reactions[29, 32]

The oxidative Heck reaction differs from the Mizoroki-Heck reaction in the first step of the catalytic cycle (Scheme 4).[32] Where oxidative addition of the aryl halide or triflate onto Pd(0) begins the Mizoroki-Heck cycle, the oxidative Heck mechanism commences with transmetallation of the aryl boron reagent onto Pd(II) to form intermediate **II**. Migratory insertion of the alkene substrate onto the active palladium species then occurs and *β*-hydride elimination of **III** occurs to form the product and palladium species **IV**. Reductive elimination of HX from **IV** then occurs, normally facilitated by a base to generate Pd(0) species **V** which is oxidised to reform the active Pd(II) catalyst **I**.



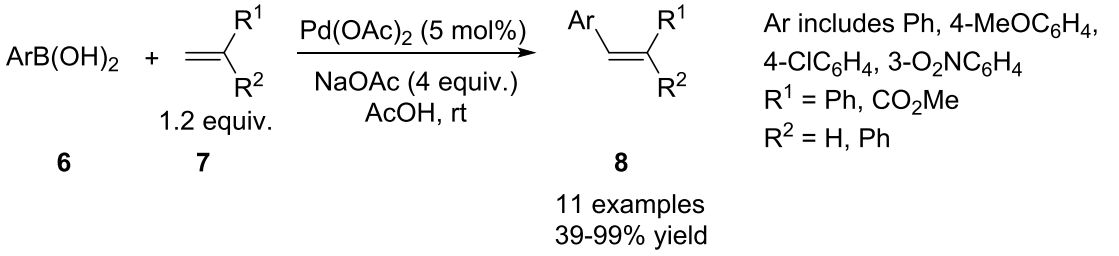
Scheme 4: Proposed mechanism for the palladium(II)-catalysed oxidative Heck coupling

Despite being less developed, the oxidative Heck reaction has a number of advantages over the Mizoroki-Heck coupling. Using readily available organoboron reagents[33] rather than aryl halides or triflates avoids the formation of stoichiometric quantities of halide salts used in the Mizoroki-Heck reaction. Additionally, oxidative Heck reactions often use mild reaction conditions, are tolerant of air and moisture and have proved to be capable of coupling challenging substrates such as cyclic enones and highly substituted alkenes.[29, 34-38] Given these advantages, the oxidative Heck reaction has become an attractive alternative option for cross-coupling compared to more established methods and has been the topic of several reviews in recent years.[29, 39, 40]

1.2.2 Development of the oxidative Heck reaction

Since the initial discovery of the oxidative Heck reaction, a number of coupling partners have been employed as alternatives to organoboron compounds. Both Jung and Mori have used arylstannanes in oxidative Heck reactions.[41, 42] Additionally, organophosphonic acids,[43] organoantimony,[44] organobismuth[45, 46] and organosilicon reagents,[47, 48] amongst others[45, 46, 49-51] have successfully been used as coupling reagents. However, organoboron reagents have become the organometallic reagent of choice for the oxidative Heck reaction due to their low toxicity, stability and availability. In recent years, considerable progress has been made in developing the oxidative Heck reaction, notably Larhed,[38, 52-54] Jung[34, 37, 41] and Sigman[55, 56] have reported pioneering work in this area.

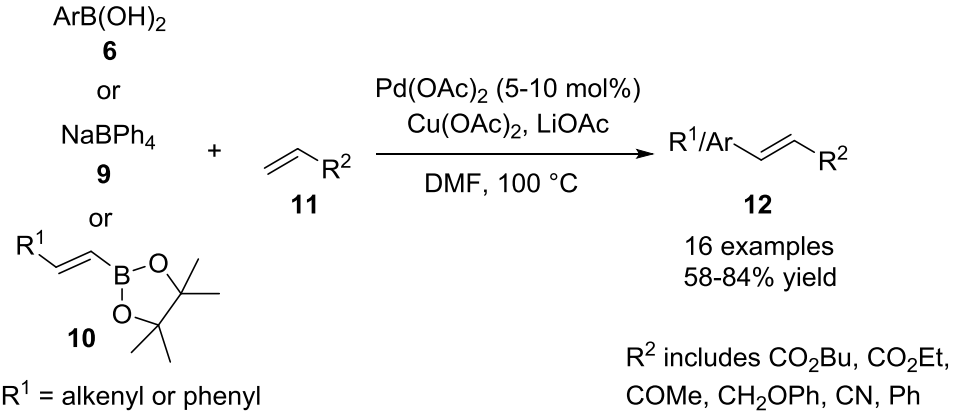
As previously mentioned, the first catalytic oxidative Heck reaction using arylboron compounds as coupling partners was reported by Uemura and Cho in 1994.[26] A variety of mono- and disubstituted alkenes **7** were screened, along with various aryl boronic acids **6** (Scheme 5). Additionally, the investigation extended to alkenylboronic acids and sodium tetraphenyl borate as coupling reagents. Moderate conditions were used (25 °C, 20 h) using sodium acetate as a base and acetic acid as a solvent. Yields of up to 99% were obtained and the reaction proceeded with excellent *E*-selectivity.



Scheme 5: First reported oxidative Heck reaction using arylboron compounds[26]

In contrast to mechanisms proposed in subsequent papers published on the oxidative Heck reaction (mechanism illustrated in Scheme 4), Uemura and co-workers suggested the reaction is Pd(0) catalysed. Reduction of Pd(II) to Pd(0) is followed by a Mizoroki-Heck type catalytic cycle with *oxidative addition* of the boronic acid to the Pd(0) species. However, mechanistic studies were not carried out to confirm this hypothesis and later publications on reactions between arylboronic acids and alkenes suggest this is the first example of an oxidative Heck reaction.

In 2001, Mori and co-workers reported an oxidative Heck reaction of alkenes and organoboron reagents catalysed by Pd(II) (see Scheme 4 for catalytic cycle)[57] as opposed to the Pd(0) pathway proposed by Uemura.[26] Copper(II) acetate was used as a reoxidant and *N*,*N*-dimethylformamide as the solvent. A range of organoboron reagents (boronic acids **6**, tetraphenylborate **9** and pinacol esters **10**) and alkenes **11** were screened to give moderate to good yields of the desired coupling products **12** and good *E*-selectivity (Scheme 6).



Scheme 6: Pd(II)-catalysed oxidative Heck coupling of alkenes with arylboron compounds and $Cu(OAc)_2$ as an oxidant

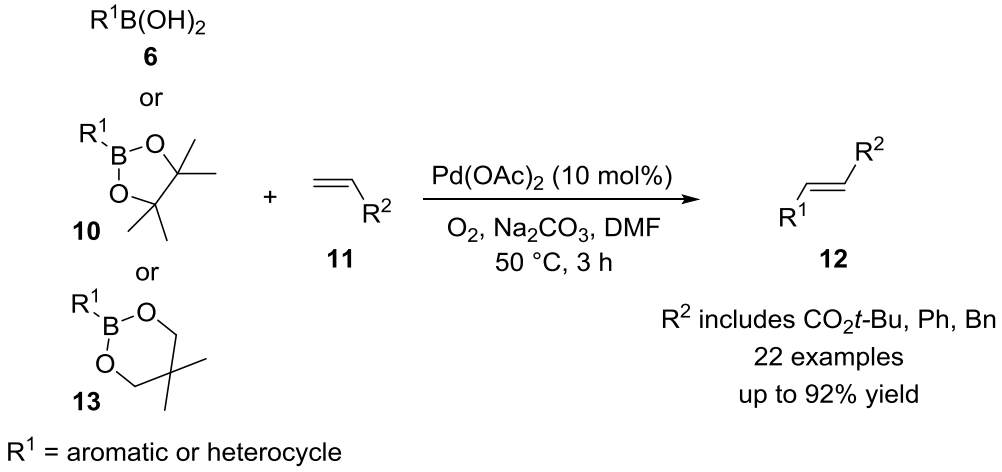
Since these initial reports on the oxidative Heck reaction, various developments have been published which will be discussed in more detail in the following parts of this review.

1.2.3 Use of oxidants in the oxidative Heck reaction

A range of oxidants have been reported to be effective in the oxidative Heck reaction.[29, 58] Copper(II) salts[6, 20, 57] and benzoquinone[59-62] were perhaps the most widely used in earlier work, although silver acetate[63] and nitroxides[64, 65] have also been used. Recent developments of the oxidative Heck reaction have resulted in the use of greener oxidants, avoiding producing metal salts or toxic hydroquinone as side products. Molecular oxygen[66-68] and even air[38, 54] have been found to be effective for reoxidation of Pd(0) to Pd(II) in oxidative Heck reactions in recent studies.

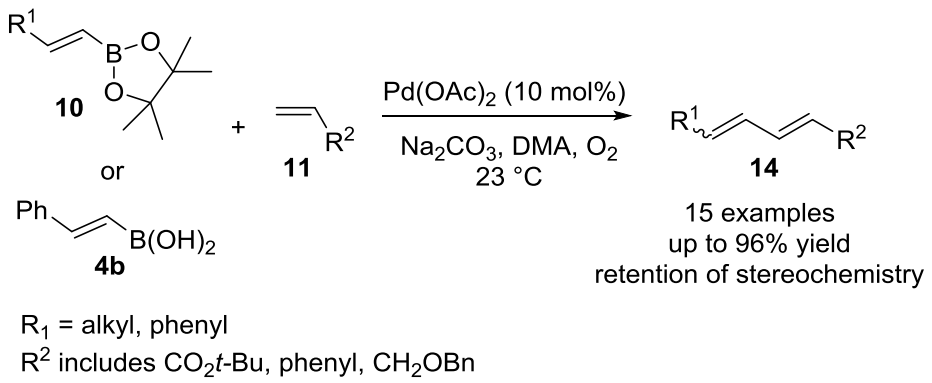
In 2003, Jung and co-workers first reported the use of molecular oxygen as an oxidant in the oxidative Heck coupling of organoboron reagents with alkenes and demonstrated that oxygen would promote the palladium(II) catalytic pathway and suppress competing

Pd(0) catalysis (Scheme 7).[66] Prior to this, Jung and co-workers had successfully used oxygen as the oxidant in the Pd(II) catalysed reaction between olefins and arylstannanes.[41] Optimisation of reaction conditions was carried out using butyl acrylate and phenylboronic acid. A number of different mono-substituted olefin substrates **11** (and two disubstituted examples) were screened (electron-donating and electron-withdrawing) along with various heterocyclic and aryl boronic acids **6** and esters (**10** and **13**). Good to excellent yields of the coupling product **12** were obtained with high *E*-selectivity. Arylboronic esters **10** and **13** were found to perform well and less homocoupling of the arylboron compounds and phenol formation was observed compared to when boronic acids **6** were used.[66]



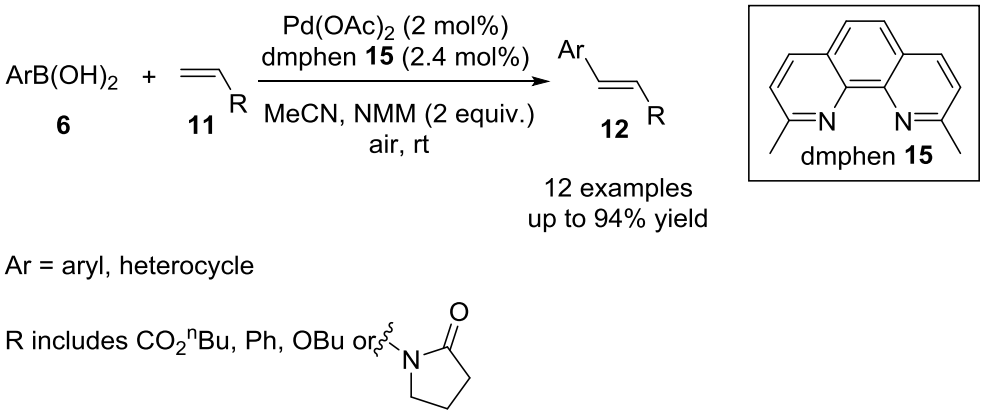
Scheme 7: First oxygen promoted oxidative Heck coupling of organoboron reagents and alkenes[66]

Jung expanded his work in this area by also investigating the oxidative Heck reaction of alkenes with alkenylboron compounds, again with molecular oxygen as an oxidant (Scheme 8).[69] A variety of alkenylboron compounds and mono- and disubstituted alkene substrates **11** were tolerated to afford *E,E*-dienes **14** in high yields and selectivities. The geometry of the alkenylboron compounds was also retained during the catalytic process.[69]



Scheme 8: Oxygen promoted oxidative Heck coupling of alkenyl boron compounds with alkenes[69]

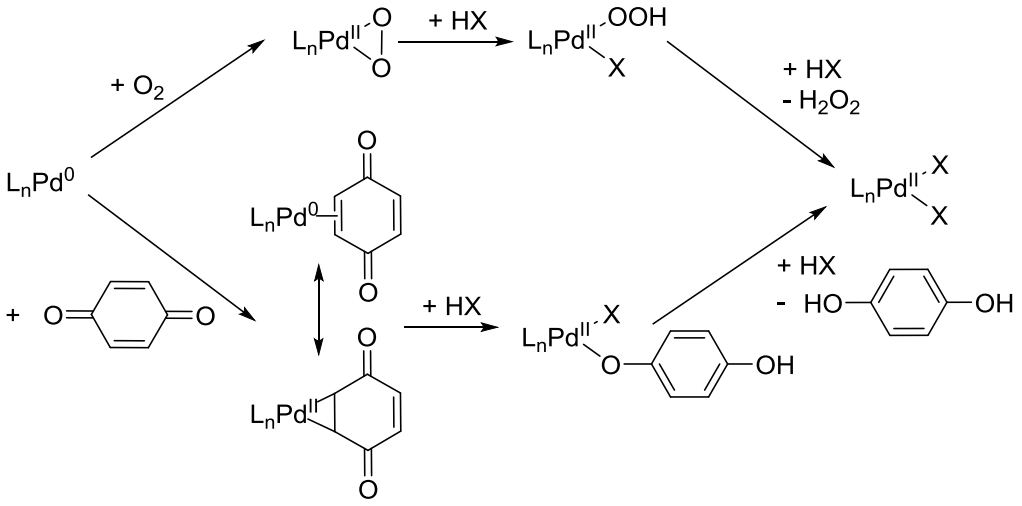
In 2006, Larhed and co-workers reported a successful open-air catalytic oxidative Heck reaction (Scheme 9).[38] Using palladium(II) acetate (2 mol%) and 2,9-dimethyl-1,10-phenanthroline **15** as the ligand, arylation of electron-rich and deficient olefins **11** was carried out at room temperature, using NMM (*N*-methylmorpholine) and under open air without the need for an additional oxidant.



Scheme 9: Open air oxidative Heck reaction of arylboronic acids and alkenes using dmphen as a ligand

A wide range of aryl and heterocyclic boronic acids **6** were tolerated in addition to alkenes **11** bearing ester, ether, amide and phenyl substituents. The reactions were carried out at both room temperature and 80 °C and yields were not temperature dependent for the majority of substrates. However, reaction times were considerably shorter at elevated temperature.

Since these initial reports, molecular oxygen has been a common oxidant in oxidative Heck reactions. Stahl and workers have published a number of reports examining the mechanistic aspects of oxidation in palladium catalysed reactions specifically focussing on benzoquinone and molecular oxygen.[59, 67, 70] Mechanistic studies indicated that the oxygenation and alkene-substitution reactions with Pd(0) have distinct similarities – the mechanism proposed by Stahl and co-workers for reactions between Pd(0) and benzoquinone, or dioxygen is shown in Scheme 10.[59]



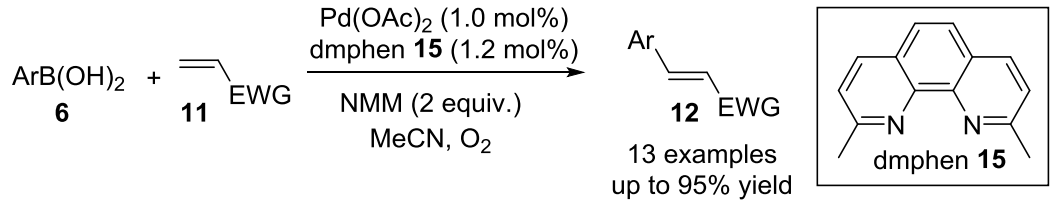
Scheme 10: Oxidation of palladium(0) by molecular oxygen or benzoquinone[59]

1.2.4 Ligand-based oxidative Heck reactions

The presence of ligands is necessary in many examples of the oxidative Heck reaction since in the absence of ligands, palladium(0) species aggregate to unreactive palladium clusters and thus retard the coupling reaction.[34] Ligands not only stabilise the catalyst and thus prevent the aggregation of palladium(0), but also increase the regio- and stereoselectivity of the reaction. Bidentate nitrogen ligands are the most versatile ligands for these reactions given their ability to facilitate the reoxidation of palladium(0) to palladium(II) by molecular oxygen, in addition to their low cost and high air- and moisture-stability in comparison to phosphine ligands.[29] Despite this, both nitrogen- and phosphine-based ligands have been used in the oxidative Heck reaction in recent years.

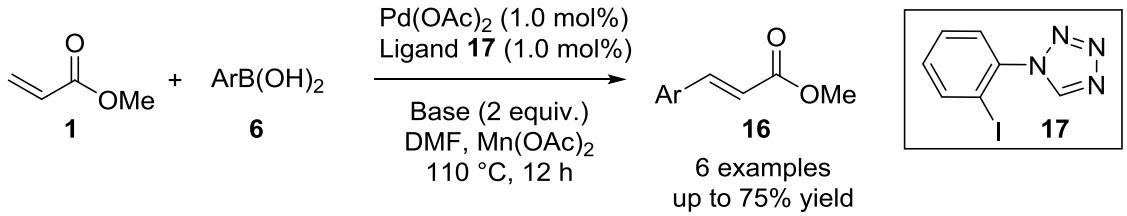
Larhed and co-workers were the first to report the use of a ligand to stabilise the catalyst in an oxidative Heck vinylation (Scheme 11).[53] It was found that using a palladium(II)

acetate catalyst, 2,9-dimethyl-1,10-phenanthroline ligand **15** (dmphen) and *N*-methylmorpholine as a base in the presence of oxygen in acetonitrile, coupling of various arylboronic acids **6** with electron-poor alkenes **11** could be achieved. Using dmphen as a ligand enabled the catalyst loading to be reduced from 10 mol% to 1 mol%. Good diastereo- and regioselectivity was observed with a number of alkenes and a diverse range of boronic acids were used with nitro, keto, bromo and iodo functionalities. Yields were excellent for electron-rich boronic acids and moderate to good when *meta*-substituted electron-poor boronic acids were used. However, *para*-substituted electron-poor arylboronic acids were inactive.[53]



Scheme 11: Pd(II)-catalysed coupling of arylboronic acids and electron-poor alkenes using dmphen as a ligand[53]

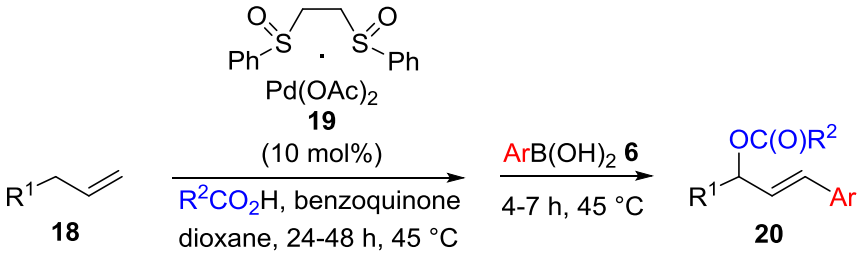
In 2004, Oh and co-workers developed a tetrazole ligand **17** for use in Heck reactions (Scheme 12).[71] During the course of their investigations, aryl boronic acids rather than aryl halides were also investigated. The ligand was also found to be compatible with the relatively harsh oxidative Heck conditions used for the reaction (110 °C, base, DMF, 12 h) and moderate to good yields (**16,** up to 75%) were obtained with a range of aryl boronic acids **6** and methyl acrylate **1** as the substrate, with $Mn(OAc)_2$ as an additive.



Scheme 12: Oxidative Heck reaction using a tetrazole ligand

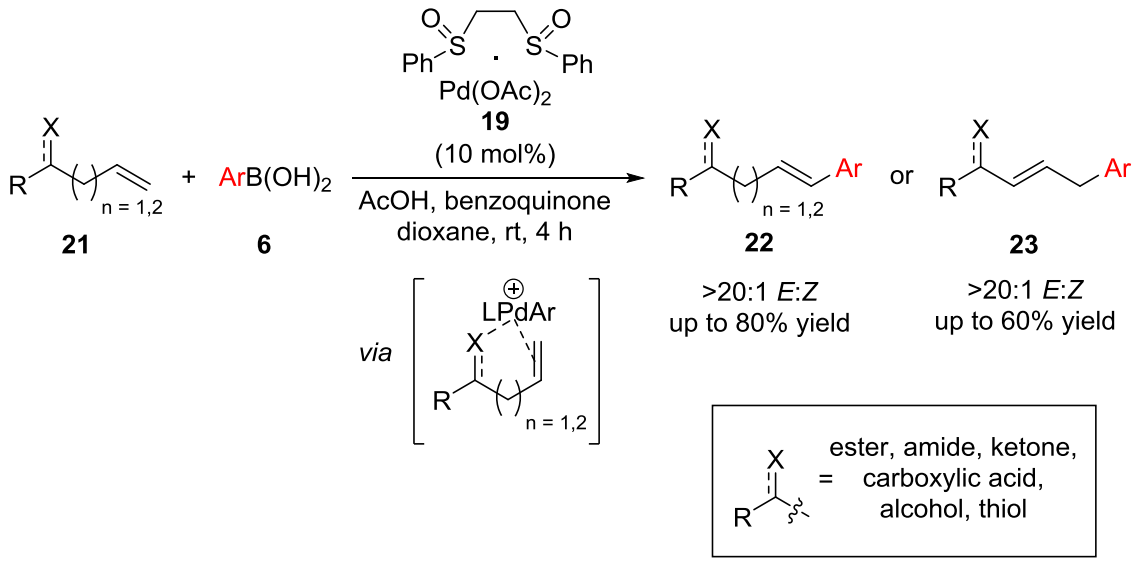
In a study by Jung and co-workers primarily focussing on developing a base-free oxidative Heck reaction (which is discussed in section 1.2.5, Scheme 17), using a ligand was found to help to stabilise the catalyst. Various bidentate phosphorus- and nitrogen-ligands were screened and although all of the ligands prevented catalyst precipitation, not all of the ligands gave good yields. For instance, using 2,2'-bipyridine gave good yields whereas 4,4'-bipyridine did not yield product. Pd-nitrogen chelating length, coordination angle and steric environment were all found to affect the reaction outcome.[34]

In 2006, White and co-workers reported a one-pot allylic C-H oxidation followed by a vinylic C-H arylation of *α*-olefins **18** (Scheme 13).[72] The reaction was carried out using a Pd(II)/sulfoxide catalyst **19** which was found to be an effective ligand in earlier work carried out by the group which focussed solely on allylic C-H oxidation.[73]



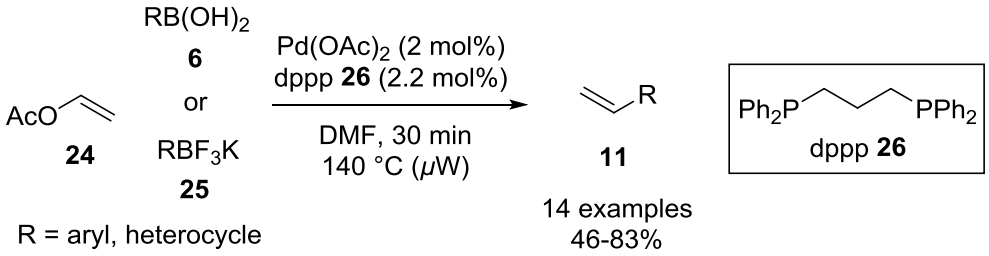
Scheme 13: Sequential allylic C-H oxidation/vinylic C-H arylation using a Pd(II)/sulfoxide catalyst

This methodology was taken further and the first oxidative Heck step in the reaction was examined in more detail in a later publication.[74] Using the aforementioned Pd(II)/sulfoxide catalyst **19**, a chelate controlled intermolecular oxidative Heck reaction was carried out on a range of olefin substrates **21** with oxygen and nitrogen functionalities (Scheme 14). Selectivities were excellent for substrates where a 5 or 6-membered chelate ring could be formed with the catalyst, yielding internal alkene product **22** selectively. A distal carbonyl functionality that would require a 7-membered chelate ring exhibited similar selectivity to unsubstituted olefins and also forms **22** predominantly although selectivity dropped. A switch in selectivity was observed when *β*,*γ*-unsaturated esters were reacted with strongly electron-deficient aryl boronic acids. This provided a facile route to the corresponding *α*,*β*-unsaturated carbonyl compounds (**23**).



Scheme 14: Chelate-controlled intermolecular oxidative Heck reaction

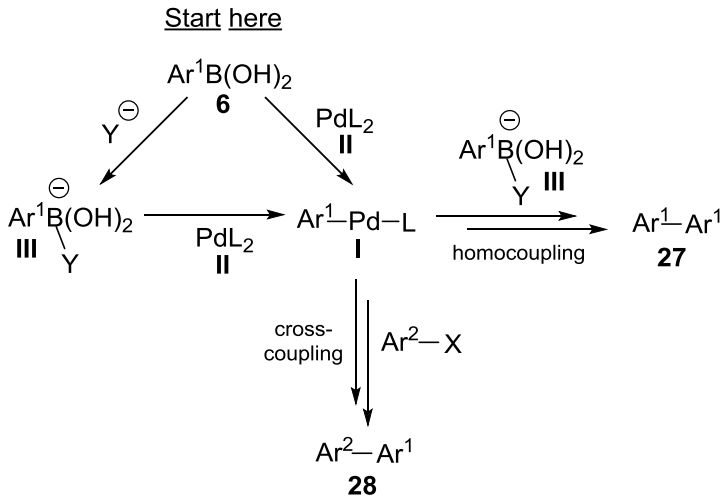
Despite the preference for nitrogen ligands in oxidative Heck reactions due to the propensity for phosphine ligands to oxidise,[75] oxidative Heck reactions using phosphine ligands have been reported.[36, 76, 77] In 2009, Larhed and co-workers reported the synthesis of styrenes *via* a vinylation of arylboronic acids **6** and aryltrifluoroborates **25** using a Pd(II)/dppp catalyst (Scheme 15).[76] Using vinyl acetate **24** as the substrate, no base or external oxidant was found to be necessary since *β*-acetate elimination during the catalytic cycle regenerated the active Pd(II) species. A number of nitrogen and phosphorus ligands were screened and dppp (1,3-bis(diphenylphosphino)propane) **26** was found to be the most effective. Additionally, an inert atmosphere was not necessary and moderate to good yields were obtained of various styrene derivatives **11**.



Scheme 15: Vinylation of organoboron compounds using a Pd(II)/dppp catalyst

1.2.5 Use of base in the oxidative Heck reaction

Bases can play a key role in palladium-catalysed cross-coupling reactions (Scheme 16). By facilitating the transmetallation of organoboron compounds **6** to organopalladium species **I** *via* organoborate salts **III** the reaction is accelerated which in turn accelerates the coupling process to form **28**. However, an additional consequence is the formation of homocoupling by-products **27** due to the high reactivity of the borate salts.[*29, 78]

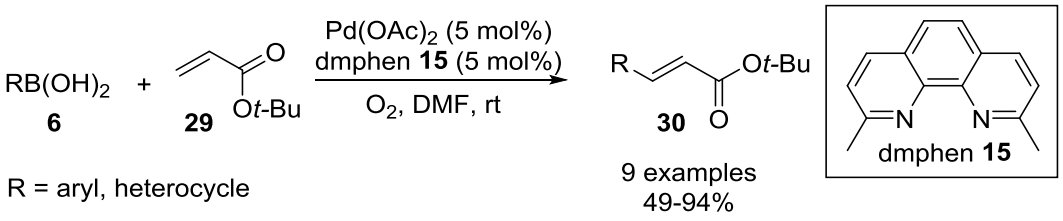


Scheme 16: Role of base in the oxidative Heck reaction

In order to avoid the formation of reactive borate salts and thus minimise homocoupling, Jung and co-workers developed a base-free oxidative Heck reaction.[34] Jung reported that organoboron reagents and olefins could be successfully coupled under mild conditions, in the absence of base, using amine ligands to stabilise the catalyst. Molecular oxygen was used as the oxidant and DMF as the solvent. In this extensive study, a plethora of substrate (substituted olefins) and organoboron reagent (aryl and alkenyl) combinations were studied and coupling was achieved in excellent yields. Specifically, for the coupling of aryl or heterocyclic boronic acids **6** with *tert*-butyl acrylate **29**, yields of up to 94% of the coupling product **30** were obtained under mild conditions and were not found to be affected by the electronics of the arylboron coupling partner. Initial optimisation studies found homocoupling of the boronic acid and formation of phenol to be an issue, yet when 2,9-dimethyl-1,10-phenanthroline **15**

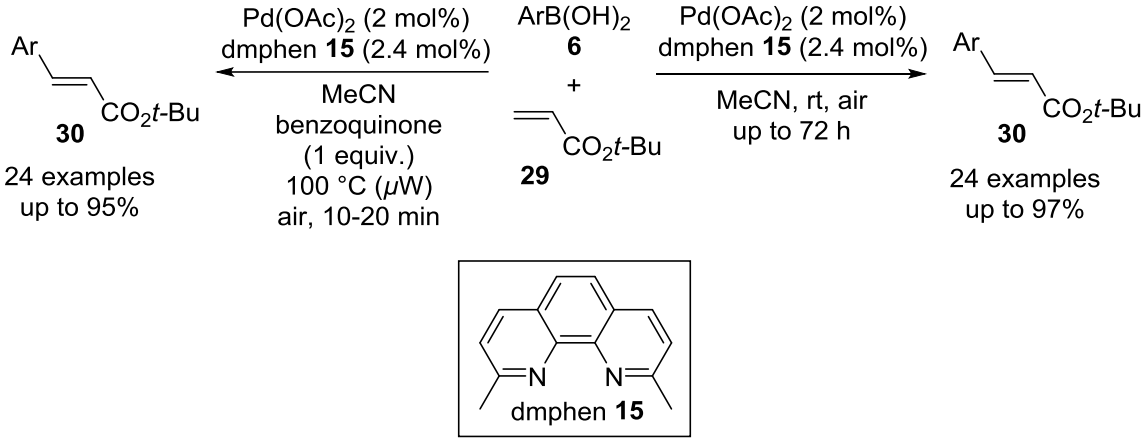
[*]Alternatively, more recent investigations have indicated that the base could be activating the palladium intermediate **I** rather than the boronic acid to form the oxypalladate complex. See references 78 and 79 for further information.

was employed as a ligand, formation of these side products was minimised, yields were enhanced, and milder conditions could be employed (Scheme 17).



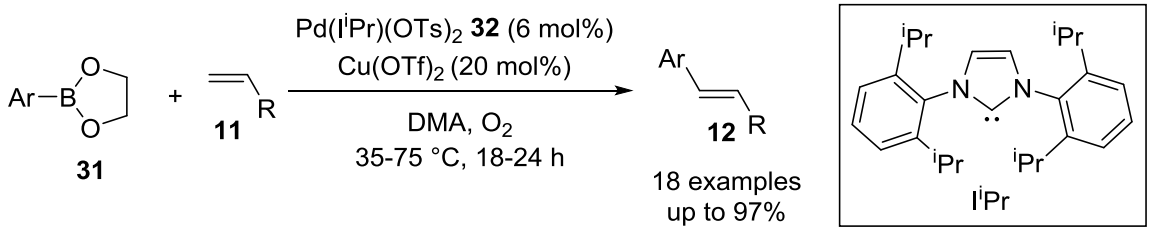
Scheme 17: Base-free oxidative Heck reaction of arylboronic acids with *tert*-butylacrylate[34]

In 2007, Larhed and co-workers also reported a base-free oxidative Heck reaction with *tert*-butyl acrylate **29** and aryl boronic acids **6** (Scheme 18).[54] Reactions were carried out under mild conditions, at room temperature and under air as the oxidant. An additional part of the study investigated the effect of microwave heating. *Para*-Benzoquinone was used as the oxidant given that air was not a practical option. Microwave heating was found to maintain excellent yields and reduce reaction times to between 10 and 20 minutes. Both sets of reaction conditions were suitable for a wide range of olefin substrates bearing ester, aldehyde, amide, ether and sulfonyl groups and arylboronic acids with varying electronic properties (albeit mostly *para*-substituted aryls).



Scheme 18: Base-free oxidative Heck reaction of arylboronic acids with *tert*-butylacrylate under air[54]

Werner and Sigman also reported a mild, base-free oxidative Heck protocol in 2010.[55] *E*-Styrenyl products **12** were obtained in excellent yields and selectivities from the corresponding alkene substrate **11** and boron ester coupling partner **31** (Scheme 19).



R includes alkyl chain with ketone, amine, ester functionalities

Scheme 19: Base-free oxidative Heck reaction of electronically non-biased olefins and arylboronic esters[55]

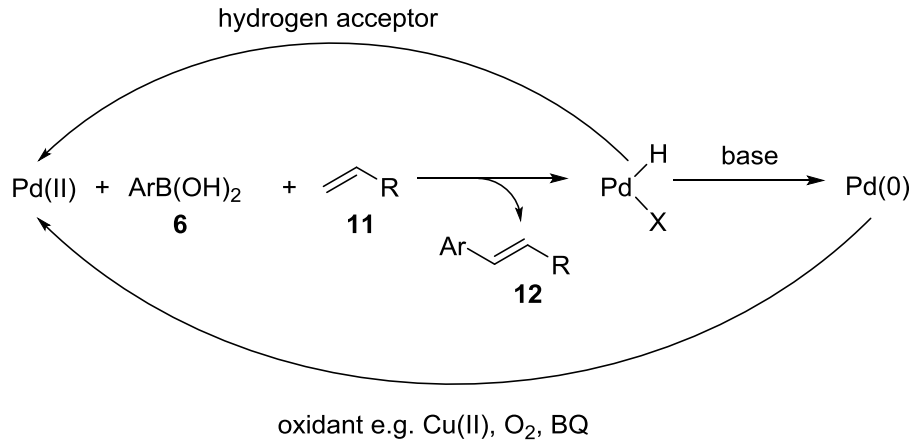
A wide variety of functional groups on the alkene substrate were tolerated (ketone, amide, alcohol, amine, ester), yet the substrates were also electronically nonbiased; the functional groups were located between 2 and 9 carbon atoms from the reactive alkene site demonstrating that high selectivity could be obtained even without specific electronic properties close to the reactive centre.[55]

1.2.6 Anaerobic oxidative Heck reactions

In addition to aerobic systems, investigation has been carried out in the area of reoxidant-free and base-free oxidative Heck reactions.

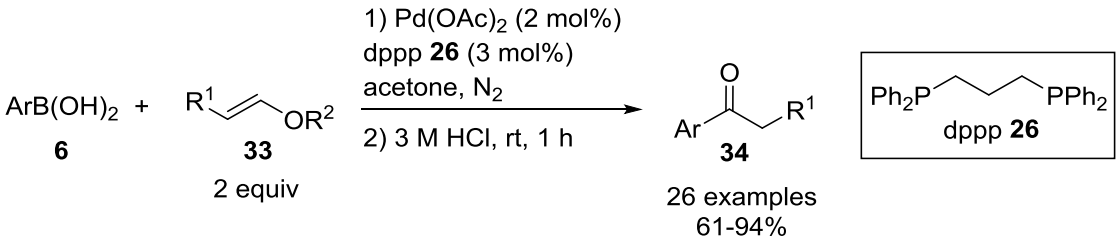
In 2008, Xiao and co-workers reported a new and efficient system for the oxidative Heck coupling of arylboronic acids with both electron-rich and electron-deficient olefins, in the absence of reoxidant and base, using acetone as a solvent (Scheme 20).[36] Removing the need for an oxidant is an obvious favourable advancement in the development of the oxidative Heck reaction.

Xiao and co-workers hypothesised that following the release of the product **12** from Pd(II) during the oxidative Heck catalytic cycle, the X-Pd-H intermediate might be intercepted by an hydrogen acceptor, which would regenerate Pd(II) without forming Pd(0) and therefore avoiding the need for traditional oxidants or base.[36]



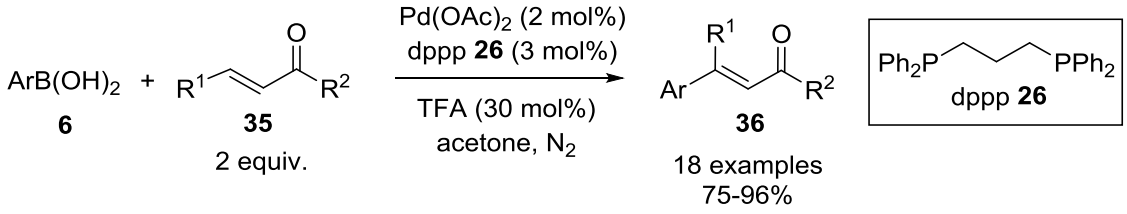
Scheme 20: Oxidative Heck coupling with and without reoxidant[36]

Various arylboronic acids **6** and alkenes **33** were screened using 1,3-*bis*(diphenylphosphino)propane (dppp) **26** as the ligand, acetone as the solvent and under a nitrogen atmosphere to afford products **34** in good to excellent yields (Scheme 21). A slight reduction in yield was observed when using *ortho*-substituted or electron-withdrawing boronic acids.[36]



Scheme 21: Oxidative coupling of various boronic acids and substituted vinyl ethers[36]

On using electron-deficient alkenes as the substrate, yields significantly reduced. However, acids were found to accelerate the reaction and addition of trifluoroacetic acid (TFA, 30 mol%) to the reactions with electron-deficient olefins furnished the coupling product **36** in excellent yield with a range of boronic acids **6** and alkene substrates **35** (Scheme 22).[36]



Scheme 22: Oxidative coupling of electron-deficient olefins and arylboronic acids[36]

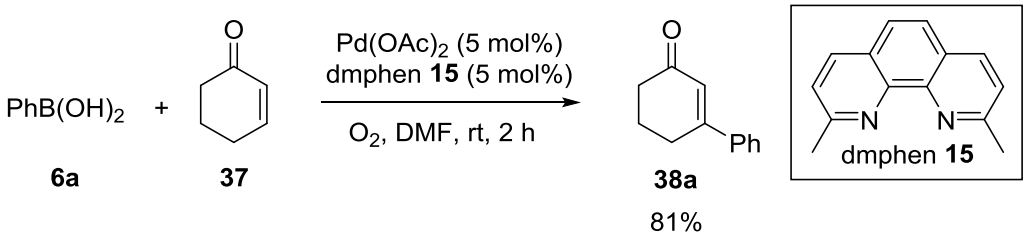
Although mechanistic studies were not discussed in detail in the report, initial ^{1}H NMR investigations did conclude that in those reactions with electron-deficient olefins, the substrate acts as the hydrogen acceptor and thus no base nor oxidant is required.[36]

In addition to the aforementioned study by Xiao and co-workers,[36] Larhed and co-workers also carried out a base and oxidant free oxidative Heck reaction, which was reported in 2009 and discussed in section 1.2.4 (Scheme 15).[76] Using phosphine ligands, vinyl acetate was coupled with various arylboronic acid derivatives in up to 84% yield using microwave irradiation as the heat source.

1.2.7 Oxidative Heck reactions on cyclic systems

Pd(0)-catalysed Heck reactions generally do not proceed well with cyclic systems particularly with cyclic enones and their derivatives, requiring harsh reaction conditions[34, 71, 80] in addition to having a tendency to form conjugate addition products instead.[50, 81] This is not necessarily surprising given that they are sterically precluded from undergoing the final *syn* β-H elimination step in the catalytic cycle.[50] This relationship between the formation of Heck-type coupling products *versus* conjugate addition products will be explored in more detail in chapter 2.

In recent years, the oxidative Heck reaction has emerged as a promising alternative for performing Heck-type couplings on cyclic systems. The conditions are milder than for traditional Heck couplings, although there are still relatively few examples reported. In work published by Jung and co-workers investigating base-free oxidative Heck reactions (*vide supra* section 1.2.5, Scheme 17),[34] 2-cyclohexen-1-one was also screened as a substrate. Initially, 1-hexenyl pinacolboron ester was found to couple with 2-cyclohexen-1-one **37** in 82% yield under base-free, mild conditions. Phenyl boronic acid **6a** was also investigated as a coupling partner and yielded the oxidative Heck product **38a** in 81% yield (Scheme 23).[34]

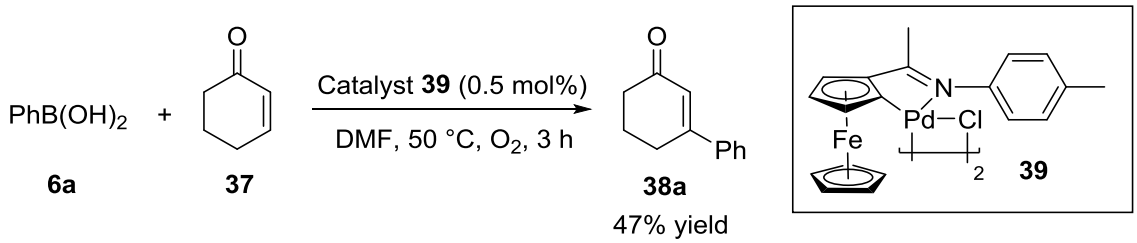


6a **37** **38a** 81%

Scheme 23: Oxidative Heck coupling of 2-cyclohexen-1-one and phenyl boronic acid[34]

Jung and co-workers suggested that a base assisted β-hydride elimination (*anti*-elimination) takes place with cyclic systems and where base is not present the ligand could also function as a base to help facilitate this process.[34] However, subsequent work published by our group (see chapter 2),[82] demonstrates that oxidative Heck reactions can be carried out under ligand- and base-free conditions. Therefore, syn β-hydride elimination is proposed as the final step of the catalytic cycle whereby isomerisation of a Pd-enolate intermediate allows this final step to take place. This is discussed further in chapter 2 (Scheme 61).

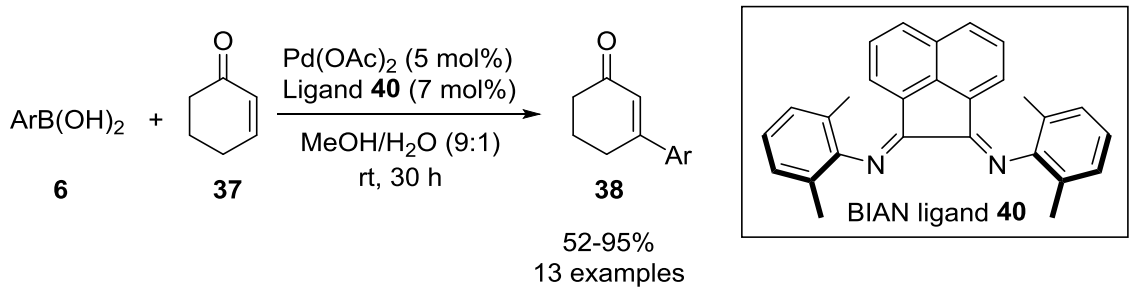
In 2010, Wu and co-workers reported a study of ligand- and base-free oxidative Heck reactions using a premade Pd(II)-ligand complex **39** (Scheme 24). Various alkenes and boronic acids were included in the study, including an example of a cyclic enone substrate (2-cyclohexen-1-one **37**), although the yield of **38a** is modest (47%).[83]



Scheme 24: Ligand and base-free oxidative Heck reaction with 2-cyclohexen-1-one as a substrate

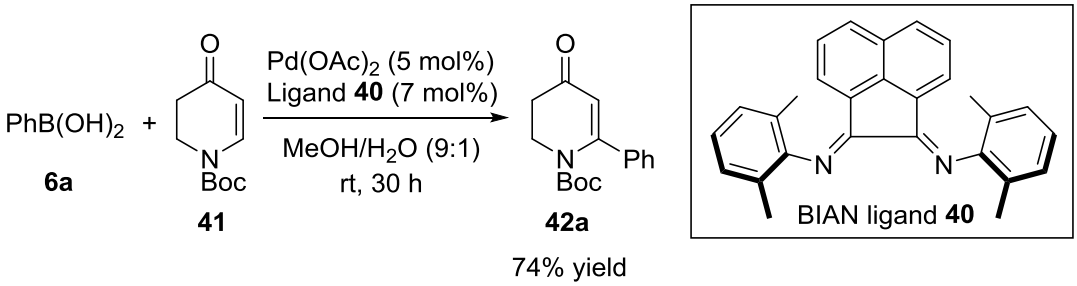
Minnaard and co-workers have also demonstrated an excellent base-free oxidative Heck protocol for functionalising 2-cyclohexen-1-one with aryl boronic acids using a Pd-diimine catalyst.[84]

Using base-free conditions and a BIAN ligand **40** (bis(imino)acenaphthene), excellent yields were obtained of arylated cyclohexenones **38** using a variety of electron-donating, withdrawing and sterically hindered aryl boronic acids **6** (Scheme 25).



Scheme 25: Base-free oxidative Heck reaction of 2-cyclohexen-1-one and aryl boronic acids[84]

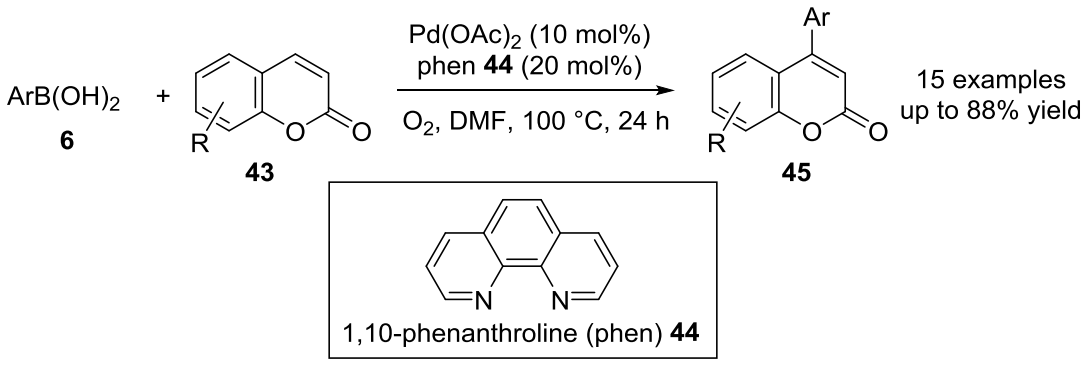
An additional small substrate scope of other enones was reported which included one other cyclic substrate, 2,3-dihydropyridin-4(1*H*)-one **41** which was arylated in good 74% yield (Scheme 26).



Scheme 26: Base-free oxidative Heck reaction of 2,3-dihydropyridin-4(1*H*)-one and phenyl boronic acid[84]

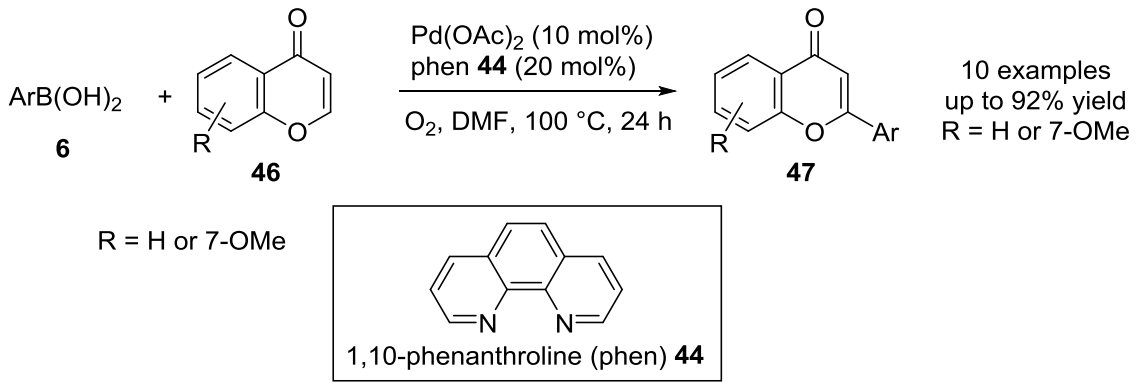
Two separate research groups published reports in early 2012 on oxidative Heck reactions using coumarins and arylboronic acids.[85, 86]

Shafiee and co-workers successfully coupled arylboronic acids to coumarin and chromenone substrates in up to 92% yield under base-free conditions and using 1,10-phenanthroline as a ligand (Scheme 27). The reactions with coumarin substrates were highly regioselective and high yielding with a range of substrates **43** and boronic acids **6**.[86]



Scheme 27: Base-free oxidative Heck reaction of coumarins with aryl boronic acids

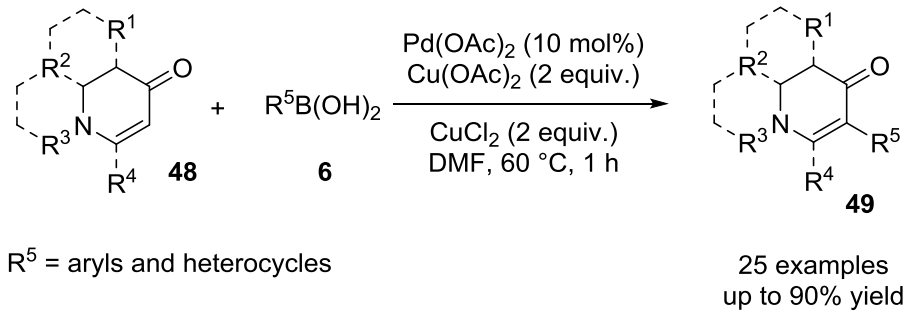
Using various chromenone substrates **46** and a range of aryl boronic acids **6** also furnished the desired oxidative Heck products **47** in excellent yield and regioselectivity (Scheme 28).[86]



Scheme 28: Base-free oxidative Heck reaction of chromenones with aryl boronic acids

In a publication by Duan and co-workers published at the same time, similar conditions are used to functionalise substituted coumarins.[85] Given some competition with the conjugate addition reaction pathway was observed, this will be discussed in chapter 2 along with other publications examining the switching between conjugate addition and Heck-type products.

Georg and co-workers have studied the Pd(II)-catalysed arylation of cyclic enaminones **48**. They have investigated a range of coupling partners in their C-H arylation work, initially using aryltrifluoroborates,[87] followed by arylsilanes.[88] More recently, work has focussed on developing a protocol using copper(II) additives and more readily accessible aryl boronic acids **6** (Scheme 29).[89] Despite the oxidative Heck-type product **49** being formed, a CH activation mechanism is hypothesised whereby a palladium-enaminone species is formed first followed by transmetallation of the aryl group onto palladium from the boronic acid, or an arylcopper intermediate.



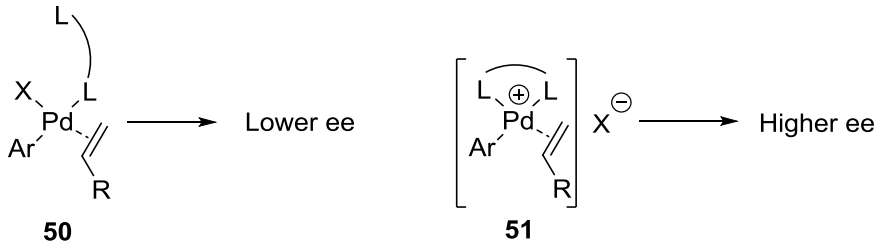
Scheme 29: Oxidative Heck-type coupling of cyclic enaminones with arylboronic acids

As is evident from the examples of oxidative Heck reactions on cyclic substrates discussed above, there are limited examples of oxidative Heck reactions on cyclic systems. Therefore there is plenty of scope to expand in this area and further advances would be highly desirable.

1.2.8 Asymmetric oxidative Heck reactions

The first examples of asymmetric Heck couplings were reported independently by Overman[90] and Shibasaki[91] in 1989 and carried out intramolecularly using cyclic substrates. Since this initial report, the enantioselective intramolecular Heck reaction has become a useful tool for synthetic chemists, for instance to construct all carbon quaternary stereocentres.[92, 93] However, the intermolecular Heck reaction on acyclic substrates has been much more challenging, with the first reported example in 2000 by Uemura and co-workers which reported a modest 17% enantiomeric excess.[94]

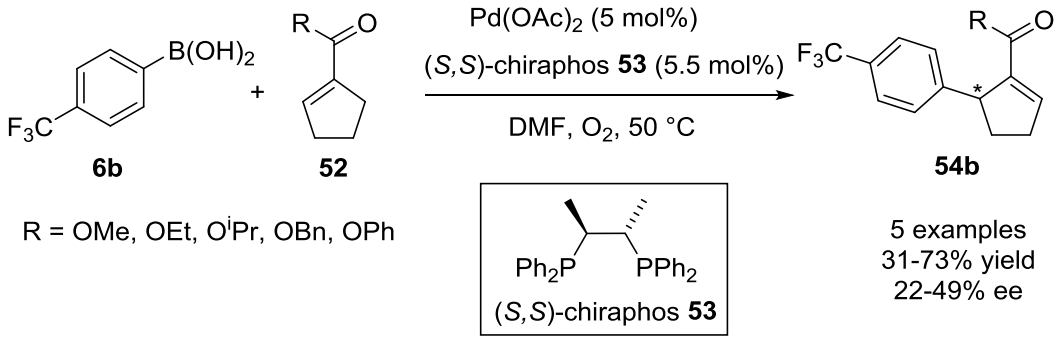
However, the enantioselective *oxidative* Heck reaction on acyclic substrates has shown considerable promise in recent years and reports have demonstrated that it can be carried out with excellent stereoselectivity, yields and often under mild conditions.[29, 32] This can be attributed to the fact that oxidative Heck reactions proceed *via* a cationic pathway (*via* species **51**, Scheme 30) rather than a neutral reaction pathway (*via* species **50**) to give higher levels of enantioselectivity.[29]



50 **51**

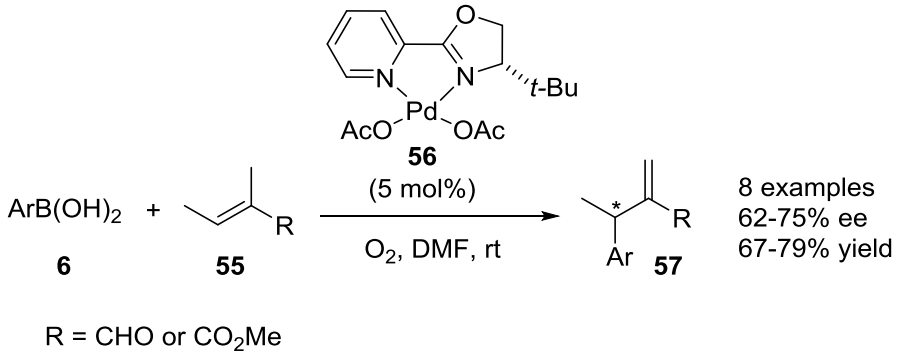
Scheme 30: Cationic and neutral reaction pathways in the oxidative Heck reaction[29]

In 2005, Mikami and co-workers published the first asymmetric oxidative Heck reaction.[95] Various chelating nitrogen- and phosphorus-ligands were screened and (*S*,*S*)-chiraphos **53** was found to be most effective (Scheme 31). Successful coupling was achieved of several cyclopentene-1-carboxylates **52** with 4-trifluoromethylphenyl boronic acid **6b** with modest to good yields and modest enantioselectivity. However, the reaction scope was limited to coupling of trisubstituted alkenes **52** with the electron-withdrawing boronic acid **6b** (a six-membered carboxylate and a cyano-substituted cyclopentene only provided trace product).[95]



Scheme 31: First enantioselective oxidative Heck reaction using (*S,S*)-chiraphos as a ligand[95]

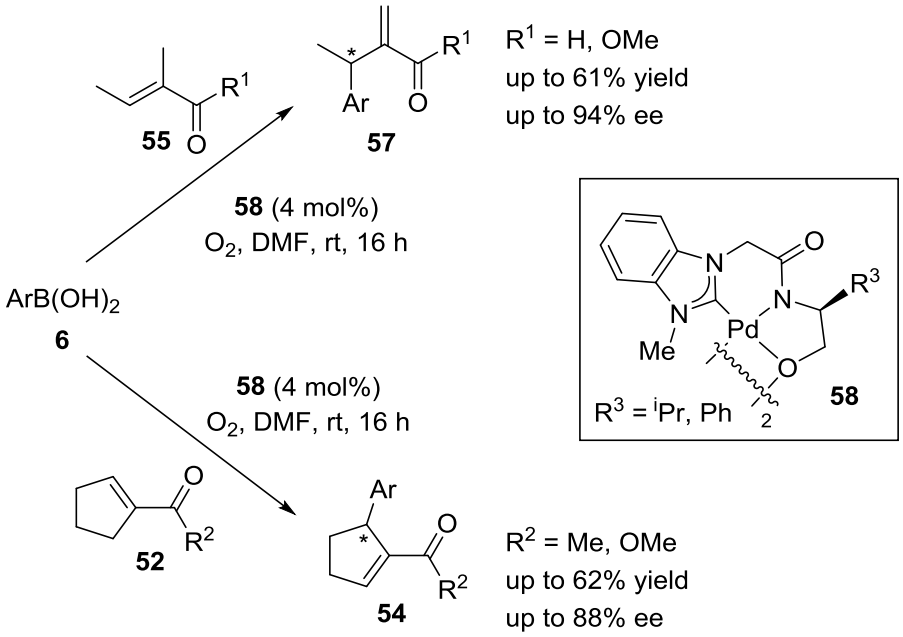
In 2007, Jung and co-workers reported an asymmetric intermolecular oxidative Heck reaction on acyclic alkenes in good yield and decent enantioselectivity (Scheme 32).[37] A ligand screen found that phosphine-based ligands were inefficient due to side reactions but nitrogen-ligands (bisoxazoline and pyridinyloxazoline) gave more promising results. After further optimisation a palladium-pyridinyloxazoline diacetate complex **56** was found to give the highest enantioselectivity and was used for a substrate screen with various electron-donating boronic acids **6**. Good yields and modest enantioselectivities of the oxidative Heck product **57** were obtained (up to 75% ee and up to 79% yield).



Scheme 32: Pd(II)-catalysed asymmetric intermolecular Heck-type reaction of acyclic alkenes

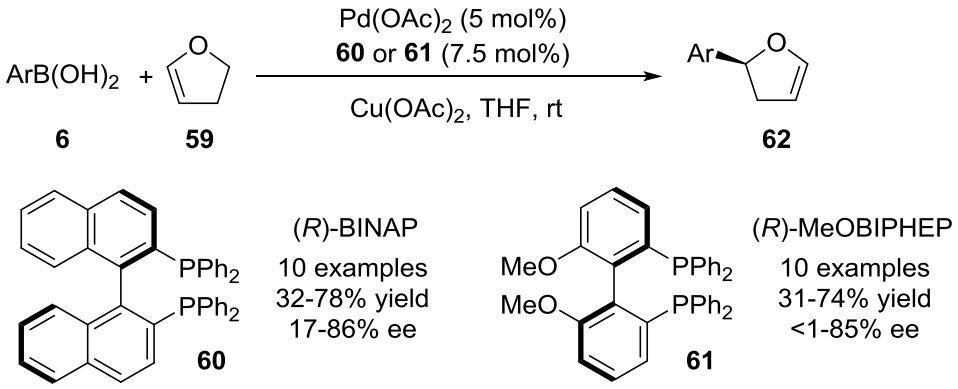
Jung continued to develop the work on enantioselective oxidative Heck reactions and reported further developments using chiral palladium complexes comprising NHC-ligands to yield excellent enantioselectivities.[96, 97] Following on from proof of concept

studies,[96] a chiral dimeric tridentate NHC-amidate-alkoxide palladium(II) complex **58** was used as a catalyst in an oxidative Heck reaction using both acyclic and cyclic substrates (**55** and **52**) coupled with aryl boronic acids **6** (Scheme 33). Whilst moderate yields were obtained, excellent enantioselectivities were observed for acyclic and cyclic substrates with a range of boronic acids with varying steric and electronic properties.[97]



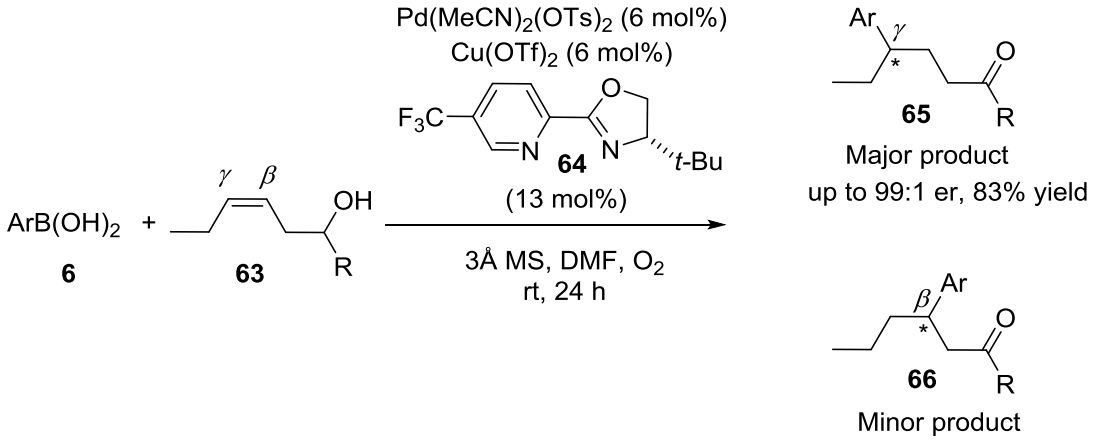
Scheme 33: Asymmetric intermolecular oxidative Heck reactions with a tridentate NHC-ligand

In 2007, Gelman and co-workers reported an enantioselective oxidative Heck of 2,3-dihydrofuran **59** with various aryl boronic acids **6** and using $Pd(OAc)_2$ with (*R*)-BINAP **60** or (*R*)-MeOBIPHEP **61** as the chiral ligand (Scheme 34).[98] Decent yields were obtained of the coupling product **62** (an isomer of the formal oxidative Heck product) with a range of both electron-withdrawing and electron-donating boronic acids. Enantioselectivity was independent of the electronic properties of the boronic acid yet the reaction was found to be sensitive to steric properties and almost no enantioselectivity was observed when *ortho*-substituted boronic acids were employed.



Scheme 34: Enantioselective oxidative Heck reaction of arylboronic acids with 2,3-dihydrofuran[98]

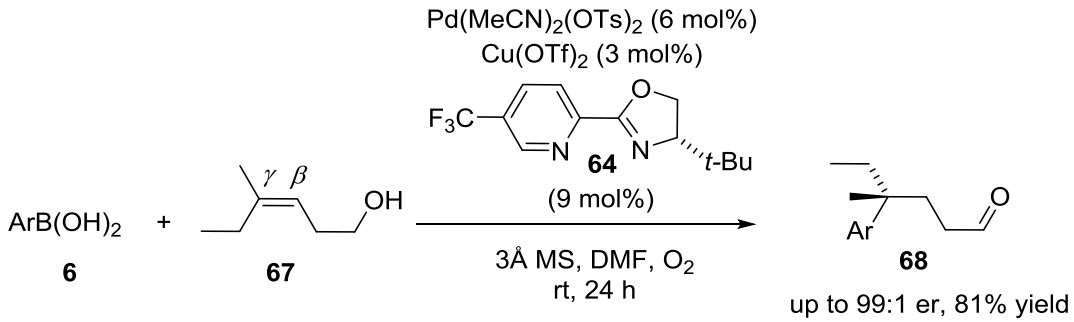
More recently, Sigman and co-workers have used oxidative Heck arylation methods to install a remote chiral centre in a molecule. Following on from work investigating enantioselective Heck arylations,[56] the study was expanded to investigate an enantioselective oxidative Heck protocol to arylate acyclic alkenyl alcohols **63** with aryl boronic acids **6** (Scheme 35).[99] Using the chiral pyridine oxazoline ligand **64**, remotely functionalised carbonyl products **65** and **66** were yielded in high enantioselectivity and site selectivity, preferentially forming the *γ*-substituted product **65** over arylation at the *β*-position to form product **66**. A range of aryl and heterocyclic boronic acids **6** with varying steric and electronic properties were screened and good yields and excellent enantioselectivities were observed.



Scheme 35: Enantioselective oxidative Heck arylation of acyclic alkenyl alcohols and boronic acids

The reaction formed the corresponding carbonyl products through a redox-relay mechanism where the alkene migrates towards the alcohol through a β-hydride elimination/migratory insertion process which results in formal oxidation of the alcohol to the carbonyl product. Additionally, selectivity of the γ-substituted product **65** over the β-substituted product **66** was observed and was found to be controlled by remote dipole interactions of the alcohol functionality. Selectivity decreased when electron-rich aryl boronic acids were used and when smaller groups at the γ-position on the substrate were present. Conversely, enantioselectivity was found to be independent of the properties of the substrate and boronic acid.

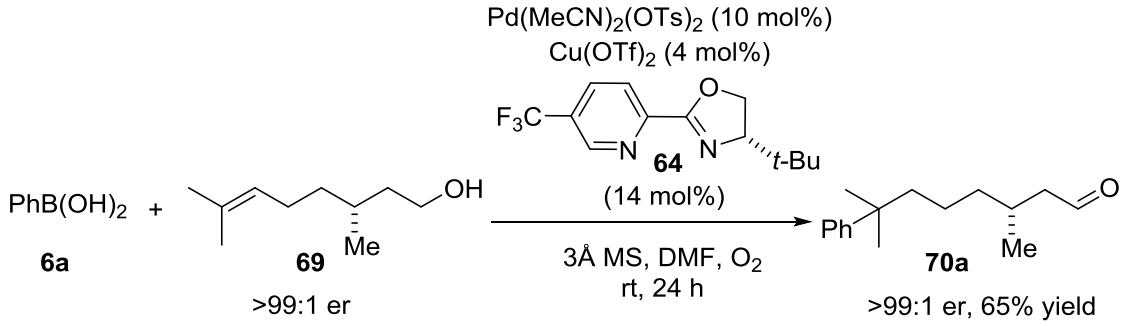
This work by Sigman and co-workers was extended in 2014 to acyclic non-conjugated trisubstituted alkenyl alcohols **67** (Scheme 36).[100] The report demonstrated that all-carbon quaternary stereocentres could be installed using this protocol at sites which are remote to other functional groups in the molecule (in this case, the alcohol moiety).



Scheme 36: Enantioselective intermolecular Heck-type reaction of trisubstituted alkenyl alcohols with aryl boronic acids

Excellent yields and enantioselectivities of the Heck-type coupling product **68** were obtained with a range of substrates **67** of differing chain lengths and boronic acids with various electronic properties. In this study, selectivity was found to be independent of the electronics of the boronic acid **6**, and substitution occurred preferentially at the more substituted carbon atom. It was hypothesised that this was due to the palladium catalyst being positioned at the less hindered carbon atom after the migratory insertion step and therefore minimising steric strain.

The study also included substrates with preinstalled stereocentres (for example **69**) and enantioselectivity was preserved during the reaction (Scheme 37).



Scheme 37: Enantioselective intermolecular Heck-type reaction of trisubstituted alkenyl alcohols with preinstalled stereocentres

1.3 Conclusions

In recent years, the oxidative Heck reaction has become a very useful tool for synthetic chemists and an attractive alternative to the Pd(0)-catalysed Heck reaction. Investigations have focussed on the development of base- and oxidant-free protocols in addition to the use of ligands which have permitted asymmetric reactions to be developed. Despite the progress in this area over the last 30 years, there is plenty of scope for further development, particularly using cyclic substrates and developing enantioselective protocols, which will be the focus of the experimental work in this thesis.

1.4 References

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Chapter 2: Ligand- and Base-Free Pd(II)-Catalysed Controlled Switching Between Oxidative Heck and Conjugate Addition Reactions

The work detailed in this chapter was carried out by the author in collaboration with a number of other members of the Lee Group: Julian Boehnke, Dr Pauline E. Glen, Steven Levey, Lisa Patrick and Dr James A. Jordan-Hore. Where work was not carried out by the author, this is clearly stated.

Chapter 2: Introduction

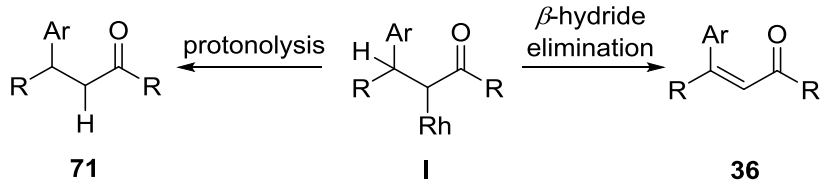
2.1 Conjugate addition versus Heck-type coupling

As has been briefly described in chapter 1, traditional Pd(0)-Heck couplings generally do not work well with cyclic enones. These substrates tend to form conjugate addition products instead, most likely due to being stereochemically precluded from undergoing the final step in the catalytic cycle – *syn* β-H elimination.[1] However, the oxidative Heck reaction has emerged as a more suitable method for forming Heck-type products with cyclic substrates, as outlined in chapter 1.[2-6]

Whilst formation of conjugate addition products as side products in Heck-type reactions and *vice versa* is relatively common,[7-9] there are limited studies which specifically focus on switching between products and the factors which may influence the reaction outcome to form one product over another. There are a select number of studies investigating rhodium- or Pd(0)-catalysed switching between conjugate addition and Heck-type products which will be discussed in this review. At the beginning of this project, there were no examples of switching between Pd(II)-catalysed oxidative Heck and conjugate addition reactions. However, after the conclusion of this project, a study was published on cyclic enaminone substrates which will be briefly discussed.[10]

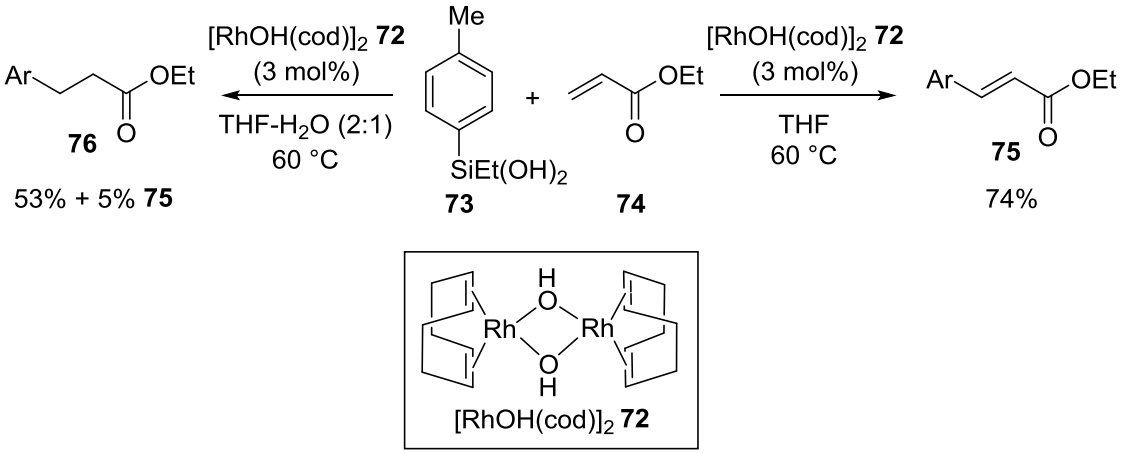
2.1.1 Switching between conjugate addition and Heck-type coupling in rhodium-catalysed reactions with acyclic substrates

Although there are few examples in the literature of controlled switching between Mizoroki-Heck/oxidative Heck and conjugate addition pathways using palladium catalysts, examples using rhodium catalysts are more common albeit most examples focus on acyclic rather than cyclic substrates. The Heck-type product **36** is formed following *β*-hydride elimination as the final step in the catalytic cycle whereas protonolysis affords the conjugate addition product **71** (Scheme 38).



Scheme 38: Formation of conjugate addition or Heck-type coupling products in rhodium-catalysed reactions

Mori and co-workers have studied the switching between Mizoroki-Heck type products and conjugate addition in the rhodium-catalysed reaction of *α*,*β*-unsaturated carbonyl compounds **74** and silanediols **73** (Scheme 39).[11]

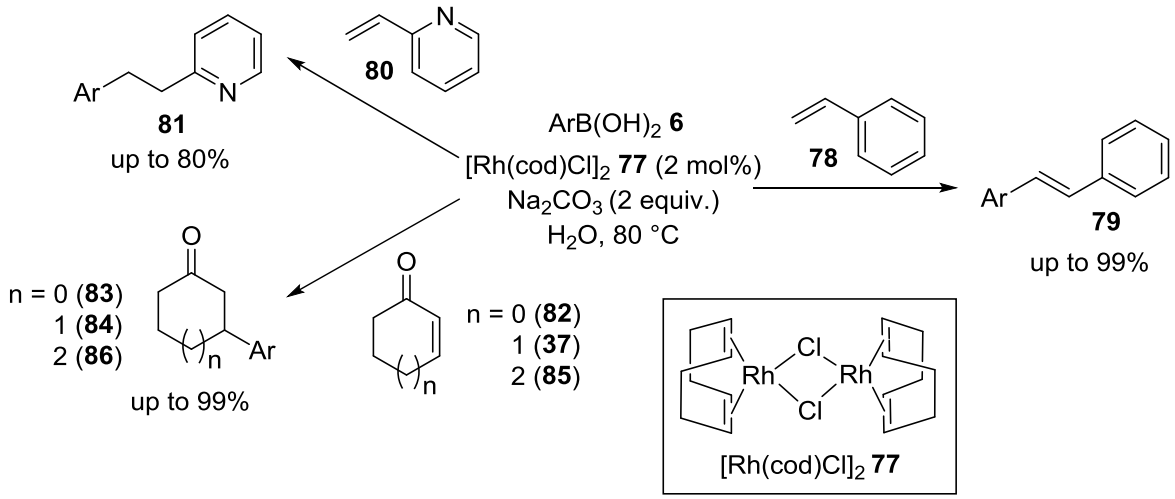


Scheme 39: Rhodium-catalysed reaction between *α*,*β*-unsaturated carbonyl compounds and silanediols to form Mizoroki-Heck type products or conjugate addition products[11]

The study found that the reaction outcome could be controlled by the use of water as a cosolvent. Using THF as the reaction solvent afforded the Mizoroki-Heck type product **75** exclusively (74% yield). Unsurprisingly, adding more water to the reaction solvent promoted protonolysis to form the conjugate addition product **76** and using a 2:1 mixture of THF:H_2O afforded almost exclusively the conjugate addition product (53% **76** with 5% Mizoroki-Heck type product **75**). Additionally, the study found that the 1,4-addition product was favoured with substrates bearing a more electron-deficient carbonyl group.

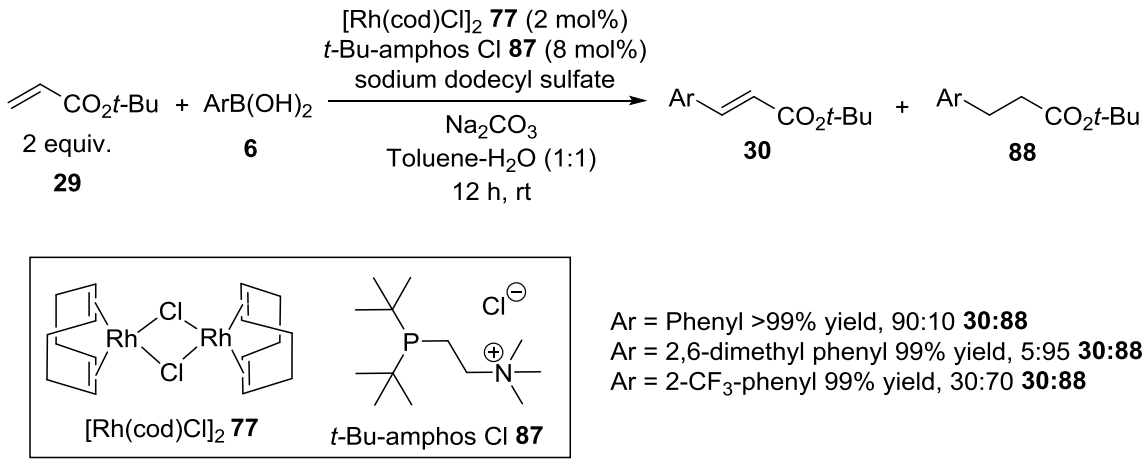
A study by Genêt and co-workers investigating rhodium-catalysed Mizoroki-Heck type reactions on acyclic α,β-unsaturated carbonyl compounds with potassium aryl trifluoroborates had similar findings to the aforementioned study by Mori. The addition of water to the reaction afforded exclusively the conjugate addition product.[12]

The outcome of rhodium-catalysed reactions between alkenes and aryl boronic acids has also been found to be substrate dependent. Lautens[13] and Genêt[14] have carried out work on such reactions in aqueous media (Scheme 40) and found that styrene substrates **78** yield the Heck-type coupling product **79** whereas vinyl heteroaromatic substrates for example **80** yield the conjugate addition product **81**. In the study carried out by Genêt and co-workers, the substrate scope was expanded to cyclic enones **82, 37** and **85** which were found to yield exclusively the conjugate addition products **83, 84** and **86** respectively.[14]



Scheme 40: Rhodium-catalysed reaction of alkenes with aryl boronic acids

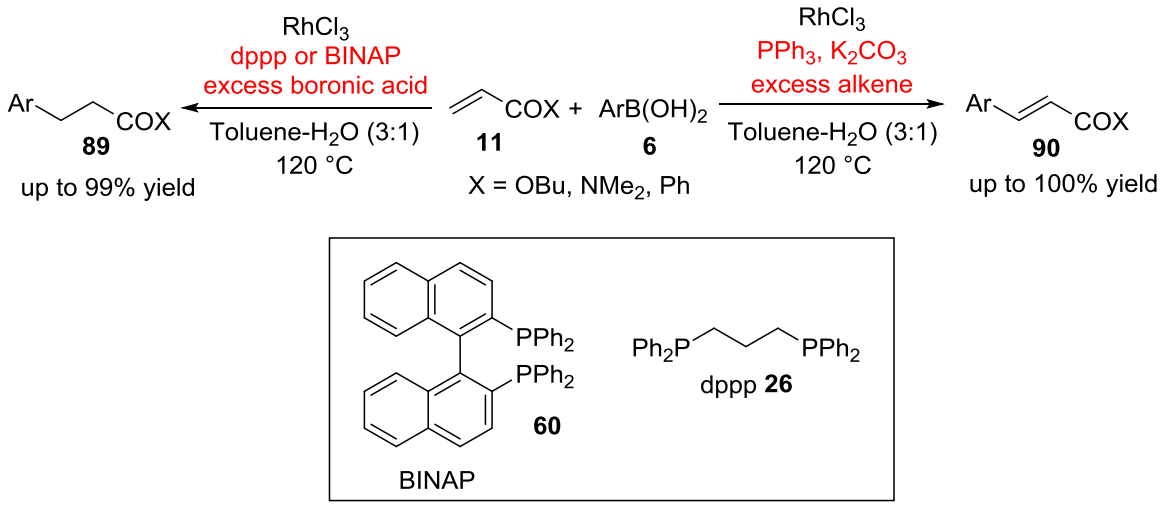
A study of rhodium-catalysed Heck-type coupling with acrylates carried out by Lautens and co-workers also found that the reaction outcome could be affected by the boron coupling partner (Scheme 41). In this study, the use of bulkier aryl boronic acids afforded the conjugate addition product **88** selectively whereas less bulky aryl groups formed Heck-type products **30**.[15]



Scheme 41: Reaction of *t*-butyl acrylate with aryl boronic acids to yield either conjugate addition or Heck-type products

Using phenyl boronic acid, the Heck-type product **30** was predominantly formed in a 80:20 ratio (>99% yield) whereas using 2,6-dimethylphenyl boronic acid switched the ratio to 95:5 conjugate addition **88** to Heck-type product **30** (99% yield). Additionally, electron-withdrawing groups on the aryl boronic acid were found to increase the formation of conjugate addition product. From these studies and considering the mechanism, it was surmised that the presence of *ortho*-substituents on the aryl boronic acid perhaps hinder *β*-hydride elimination due to steric repulsion between the substituents and the rhodium centre and thus the propensity for protodemetallation is increased and formation of the conjugate addition product is the preferential reaction pathway.

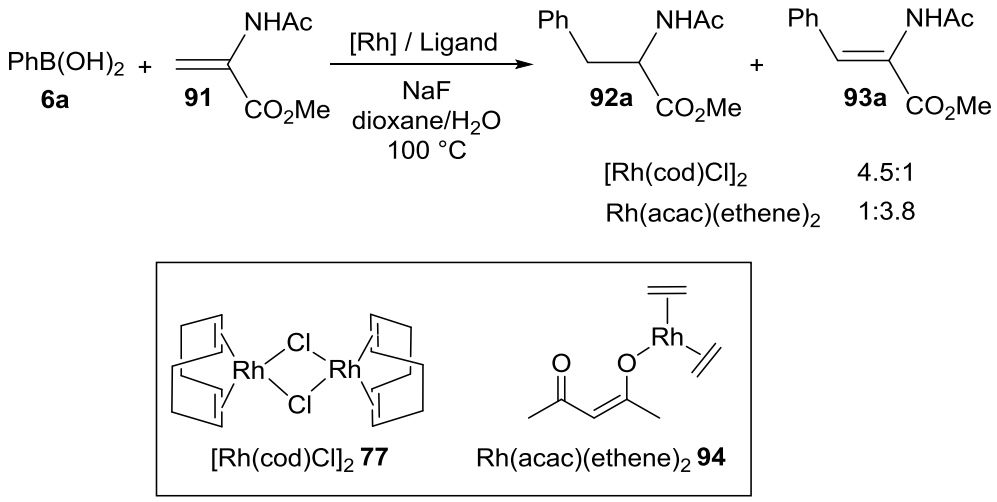
Zou and co-workers also conducted an in depth study into Heck-type coupling *versus* conjugate addition of alkenes and aryl boronic acids catalysed by rhodium (Scheme 42).[16] Their investigations examined how the choice of ligand, stoichiometry of the olefin and boronic acid, and pH of the biphasic solvent system could be tuned to selectively form either the Heck-type coupling product **90** or the conjugate addition product **89**.



Scheme 42: Tuning of reaction conditions to afford Heck-type coupling or conjugate addition product in the Rh(I)-catalysed reaction between alkenes and boronic acids

Bidentate ligands, coupled with excess boronic acid were found to promote conjugate addition (and therefore suppress the β-hydride elimination step) whereas monodentate phophines, base and excess alkene substrate promoted the Heck-type coupling reaction.

Van der Eycken and co-workers have also demonstrated that the outcome of the rhodium-catalysed reaction of arylboronic acids **6** with an α-acetamido acrylic ester **91** can be switched depending on the choice of olefin ligand (Scheme 43).[8]



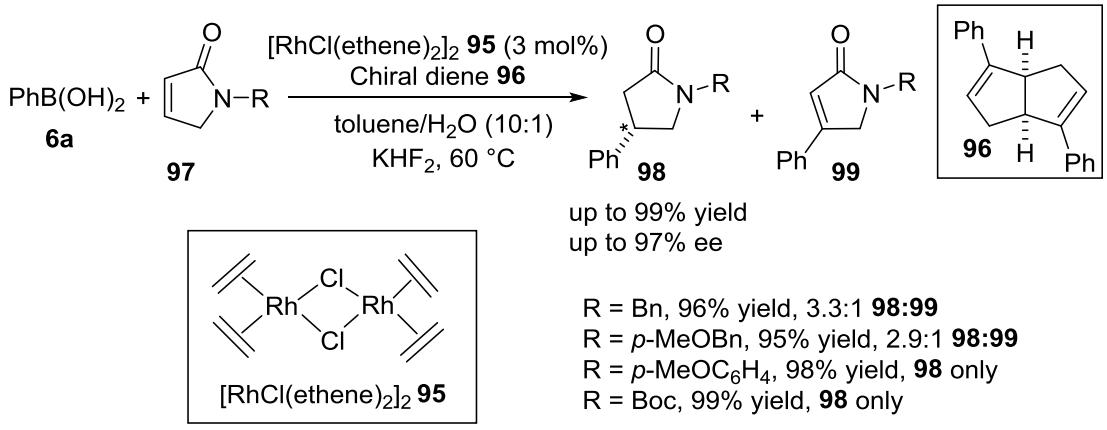
Scheme 43: Effect of ligand on the rhodium-catalysed reaction between phenyl boronic acid and α-acetamido acrylic ester

Using $[Rh(cod)Cl]_2$ **77** as the catalyst, the conjugate addition product **92a** was formed preferentially (77% yield, 82:18 conjugate addition:Heck-type product) whereas the Heck-type adduct **93a** was the major product when $Rh(acac)(ethene)_2$ **94** was employed (34% yield, 21:79 conjugate addition:Heck-type product).

2.1.2 Switching between conjugate addition and Heck-type coupling in rhodium-catalysed reactions with cyclic substrates

Whilst acyclic substrates have been investigated in this area (*vide supra*), there are few examples of studies examining switching between conjugate addition and Heck-type products of cyclic substrates.

The first reported example of competitive 1,4-addition *versus* Heck-type coupling on cyclic systems using rhodium as a catalyst was reported by Shao and co-workers (Scheme 44).[17]

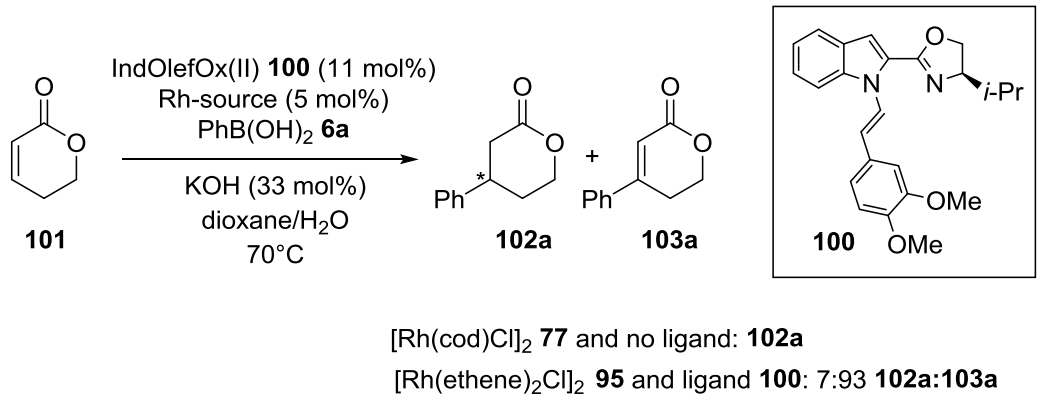


Scheme 44: Competing reaction pathways in the rhodium-catalysed reaction of unsaturated lactams with arylboronic acids

In initial optimisation work to establish suitable conditions for the 1,4-addition reaction using *α,β*-unsaturated *γ*-lactams **97** and arylboronic acids **6** it was found that the protecting group (R) used had a marked effect on the ratio of conjugate addition to Heck-type coupling products. Using benzyl or *p*-methoxybenzyl protecting groups, the 1,4-addition **98** to Heck-type product **99** ratio was found to be approximately 3:1. However, using *p*-methoxyphenyl or Boc protecting groups formed exclusively the 1,4-addition product **98**.

Franzén and co-workers have conducted a detailed investigation into the competition between conjugate addition and Heck-type coupling in the rhodium-catalysed reaction of organoboron reagents and cyclic substrates (Scheme 45).[18] Using indole-olefin-oxazoline (IndOlefOx) ligands **100** and 5,6-dihydro-pyranone or Boc-protected pyrrolidone as the substrates they examined how choice of ligand, rhodium source,

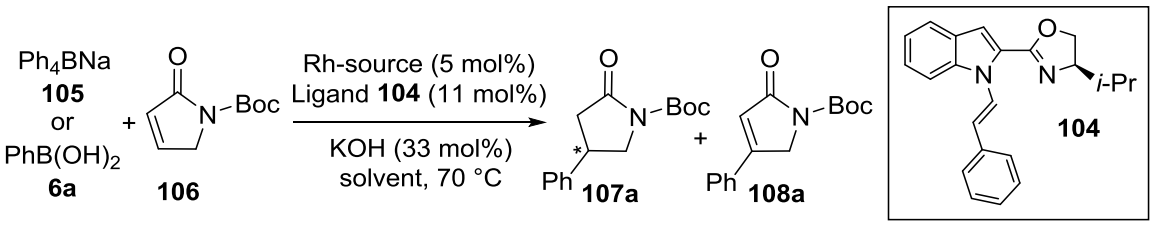
organoboron compound, substrate, solvent and amount of base used affected the ratio of conjugate addition to Heck-type product.



Scheme 45: Conjugate addition *versus* Heck coupling of aryl boronic acids with 5,6-dihydropyranone

In studies using a lactone **101**, it was found that the conjugate addition product **102a** was formed exclusively (65% yield) when $[Rh(cod)Cl]_2$ **77** was used, and in the absence of ligand. Switching the catalyst to $[Rh(ethene)_2Cl]_2$ **95** and using the IndOlefOx ligand **100** yielded a ratio of 7:93 conjugate addition **102a** to Heck-type product **103a** (67% yield, 83% ee).

Selectivity when using a lactam substrate was also found to be dependent on reaction conditions, although the outcome of the reaction could not be switched quite so effectively compared to when the lactone substrate was used (Scheme 46).



Scheme 46: Conjugate addition *versus* Heck coupling of aryl boronic acids with lactam substrate **106**

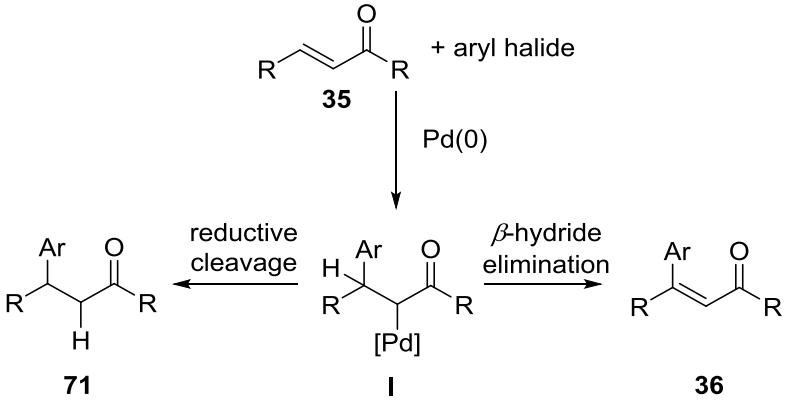
The conjugate addition product **107a** (77% yield) was formed exclusively when toluene/H_2O (3:1) was used as the solvent, along with $[Rh(cod)Cl]_2$ **77**, phenyl boronic acid **6a** and in the absence of ligand. Changing the reaction conditions to $[Rh(ethene)_2Cl]_2$ **95** and ligand **104**, accompanied with using Ph_4BNa **105** as the

coupling partner and dioxane/H_2O as the solvent yielded a 60:40 ratio of conjugate addition **107a** (84% ee) to Heck-type coupling product **108a** albeit in 20% yield.

Base was also found to affect the conjugate addition to Heck-type product ratio and unsurprisingly the amount of base used was directly proportional to the amount of Heck-type product formed with the lactone substrate. Surprisingly, base did not affect the product ratio when the lactam substrate was used.

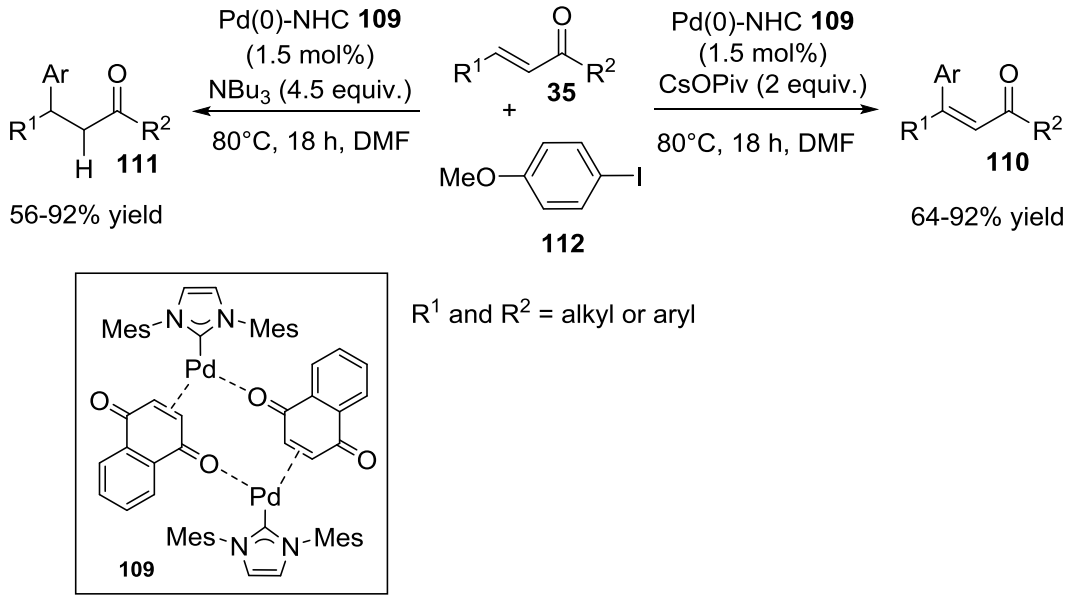
2.1.3 Switching between conjugate addition and Heck coupling in palladium(0)-catalysed reactions

Whilst switching between palladium(II)-catalysed conjugate addition and oxidative Heck reactions had not been discussed in the literature upon commencing this project, there are a few studies which examine the switching between Heck and conjugate addition products using palladium(0) as the catalyst. In these cases, the final step of the catalytic cycle is either *β*-hydride elimination to afford the Heck coupling product **36** or reductive cleavage to form the conjugate addition product **71** (Scheme 47).[19]



Scheme 47: Pd(0)-catalysed addition of aryl halides to *α,β*-unsaturated ketones to form conjugate addition or Heck products[19]

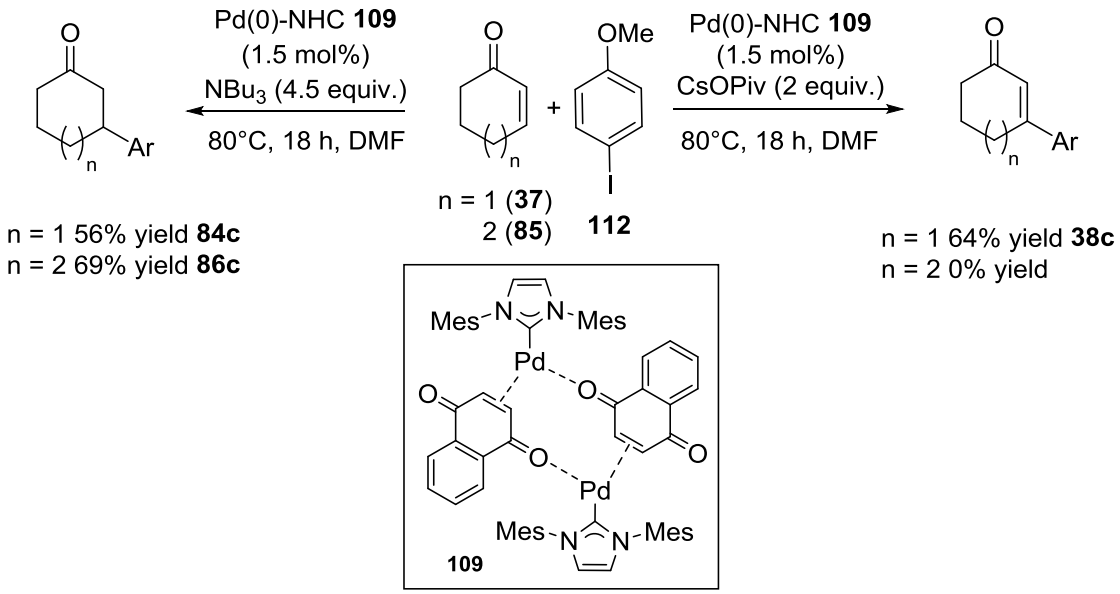
In 2011, Minnaard and co-workers investigated switching between reaction pathways of aryl iodides **112** and *α,β*-unsaturated enones **35** using a Pd(0) catalyst and an NHC ligand **109** (Scheme 48).[19] They successfully steered the reaction to conjugate addition **111** or Mizoroki-Heck **110** products by simply switching the base used to afford good to excellent yields.



Scheme 48: Switching between Heck coupling and conjugate addition products by changing the base used[19]

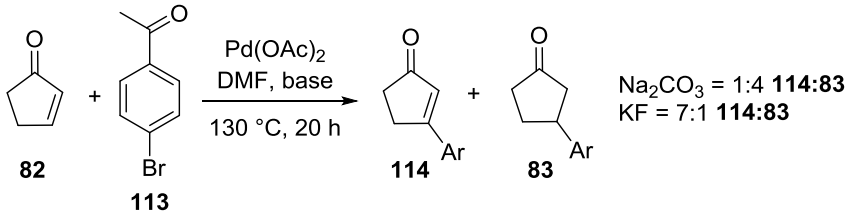
Using Bu_3N yielded the conjugate addition product **111** whereas switching the base to cesium pivalate formed exclusively the Mizoroki-Heck product **110**. In order to form the conjugate addition product, arylation of the substrate **35** would take place followed by reduction of the palladium (Scheme 48). It was therefore hypothesised that Bu_3N would serve not only as a reductant but also to keep the alkyl palladium species coordinatively saturated thus preventing *β*-hydride elimination and then forming the conjugate addition product. Minnaard and co-workers suggest that protonolysis does not take place as the final step given that there is not a proton source. Instead, reductive cleavage occurs whereby Bu_3N provides a proton *via β*-hydride elimination.

As part of this work, two cyclic systems were investigated – 2-cyclohexen-1-one **37** and 2-cyclohepten-1-one **85** (Scheme 49). Moderate switching from conjugate addition **84c** to Heck coupling product **38c** was observed with cyclohexenone **37**. However, no Heck product was formed when the 7 membered ring **85** was used as the substrate.



Scheme 49: Switching between Heck coupling and conjugate addition products with cyclic systems by changing the base used[19]

In 2009, Santelli and co-workers observed the switching between Heck and conjugate addition products in another intermolecular reaction and using cyclic enone substrates (Scheme 50).[20] Reacting aryl bromides **113** with 2-cyclopenten-1-one **82** they found that the base used affected whether the Heck **114** or conjugate addition product **83** was formed preferentially. Sodium carbonate afforded preferentially the conjugate addition product whereas switching to potassium fluoride changed the selectivity to form the Heck product as the major product. However, complete switching to one product over the other was not observed.

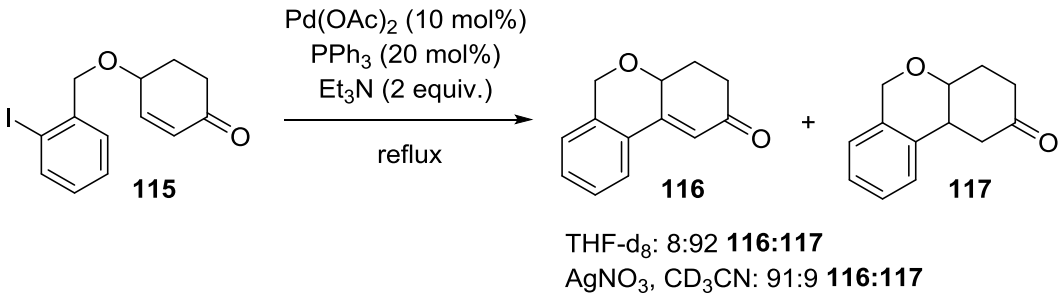


Scheme 50: Effect of base on the outcome of the Heck reaction of 2-cyclopenten-1-one and aryl bromides

Prior to this work, Pd(0)-catalysed Heck coupling on cyclic systems resulted in very low yields and/or the conjugate addition product being formed. However, Santelli developed the effective Pd(0)-catalysed method described above (Scheme 50) to

perform Heck couplings although conditions are still harsh and conjugate addition is also observed as a minor product.

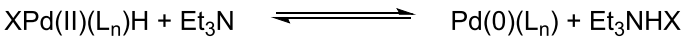
An additional example of directing the reaction outcome to form the Heck or conjugate addition product is a study carried out by Friestad and Branchaud examining the intramolecular reaction of a cyclic enone and aryl iodide (Scheme 51).[21]



Scheme 51: Intramolecular Pd(0)-catalysed reaction to yield Heck or conjugate addition product

The study found that using silver nitrate as an additive suppresses formation of the conjugate addition product **117** and the Heck product **116** is formed in a 91:9 Heck to conjugate addition ratio. Switching the reaction solvent to THF-d_8 and in the absence of any additive, the conjugate addition pathway is favoured and product **117** is formed preferentially over the Heck product **116** in 92:8 ratio. Whilst the authors did not give possible reasons for the formation of the conjugate addition product preferentially when THF-d_8 was used as the solvent, the use of additives to switch the outcome to Heck product was considered with the mechanism in mind.

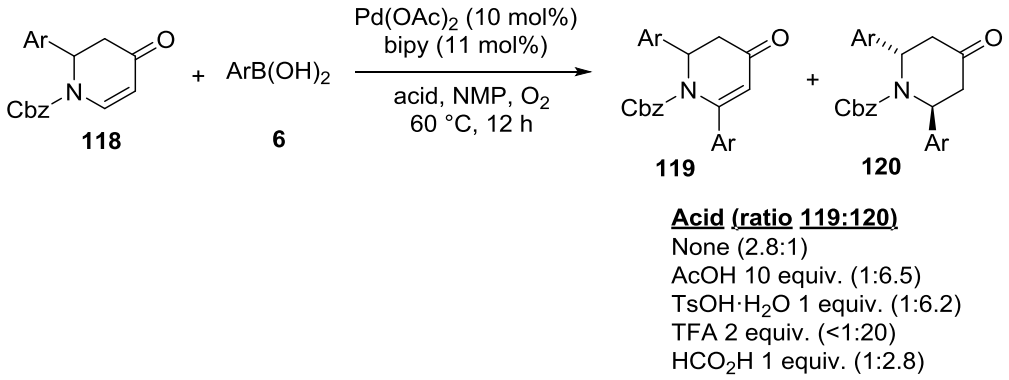
The authors surmised that given that regeneration of Pd(0) in Heck reactions occurs *via* the equilibrium shown (Scheme 52), addition of silver nitrate would scavenge HX and therefore promote formation of the Heck product.



Scheme 52: Regeneration of Pd(0) using Et_3N

2.1.4 Switching between conjugate addition and oxidative Heck coupling in palladium(II)-catalysed reactions

At the beginning of this project, to our knowledge there were no examples in the literature which focussed on the switching between Pd(II)-catalysed oxidative Heck and conjugate addition reactions. However, during the course of this thesis, and after the work detailed in this chapter had been completed and published,[22] a study was published by Georg and co-workers,[10] demonstrating that this is an area of interest for other research groups. Georg and co-workers carried out an oxidative Heck reaction on cyclic enaminones **118** with aryl boronic acids **6** and discovered that the outcome of the reaction could be switched from oxidative Heck **119** to conjugate addition products **120** by the addition of acid (Scheme 53).



Scheme 53: Pd(II)-catalysed reaction of cyclic enamines with aryl boronic acids

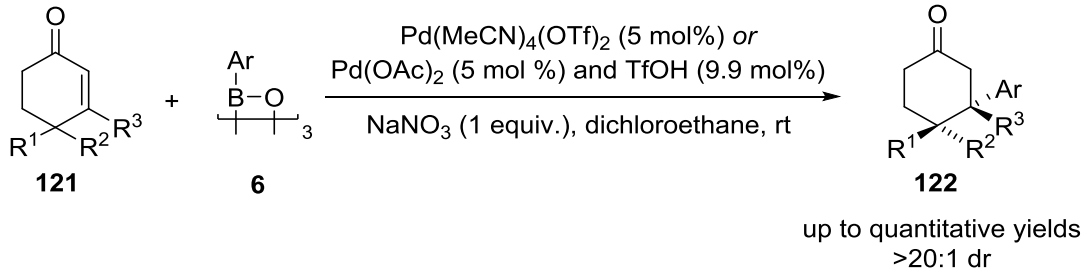
In the absence of acid, the ratio of oxidative Heck **119** to conjugate addition product **120** was 2.8:1. On adding acid, the major product switched to the conjugate addition product **120** with ratios of >20:1 conjugate addition to oxidative Heck product formed when trifluoroacetic acid was used. Unsurprisingly, the acidity of the acid used was directly proportional to the amount of conjugate addition product formed (protonolysis being favoured over syn *β*-hydride elimination).

2.1.5 Conclusion

In conclusion, competition between conjugate addition and Heck-type coupling in transition metal catalysed reactions has been documented in the literature for some years. However, specific studies examining the switching between reaction pathways and reasons for preferentially forming one product over another are rare. A small number of studies examine switching in rhodium catalysed reactions whereas investigations using palladium are scarce. Upon commencing this project, no specific studies using palladium(II) were present in the literature. Given that Pd(II)-catalysed oxidative Heck reactions have become a burgeoning area of research in recent years, a study investigating the factors which affect whether oxidative Heck or conjugate addition products are preferentially formed would be advantageous and a key advancement in this field of research.

2.2 Project aim

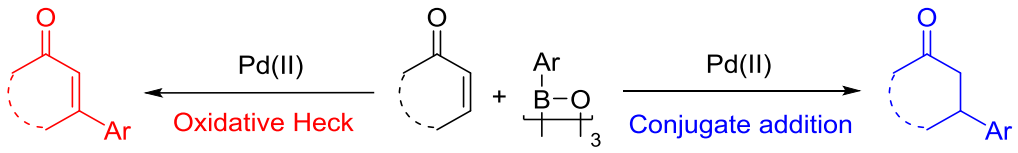
Extensive studies have been carried out in the Lee group into the Pd(II)-catalysed conjugate addition reaction of boronic acids and cyclic enones. Using a cationic, ligand-free Pd(II) catalytic system, with $NaNO_3$ as an additive, conjugate addition to sterically hindered cyclic enones (γ-, $\gamma\gamma$-, and $\beta\gamma$- substituted) has successfully been carried out in up to quantitative yields and high diastereomeric ratio (Scheme 54). These substrates are particularly challenging given their steric bulk which would make them unsuitable for rhodium catalysed conjugate addition methodology.[23] The reaction developed in the Lee group tolerates a range of aryl boroxines **6** (the dehydrated trimer of the commercial boronic acid) as the coupling partner and various substituted cyclic enone substrates **121**.[24] Following optimisation of reaction conditions, the catalyst used for the reaction was either $Pd(MeCN)_4(OTf)_2$,[25] or an *in situ* generated catalyst $Pd(OTf)_2$ (using $Pd(OAc)_2$ and triflic acid) which was found to give higher yields for more sterically hindered substrates (Scheme 54).



Scheme 54: Previous work in the Lee group - Pd(II)-catalysed conjugate additions to hindered cyclohexenones[24]

During the course of the studies into conjugate addition reactions, a solvent screen was conducted and the oxidative Heck product was found to be present when the reaction was conducted in more polar solvents. This was not necessarily surprising given that the conditions for oxidative Heck and conjugate addition reactions are often similar and therefore forming one product selectively over the other can be difficult.

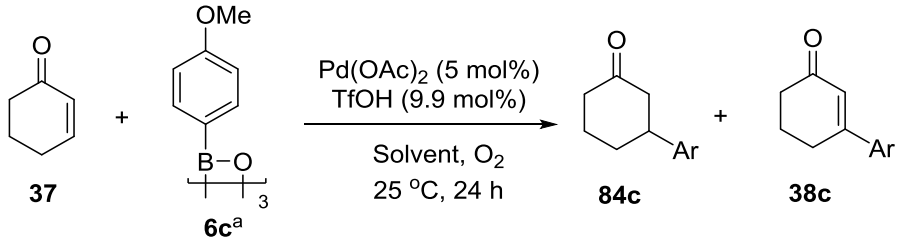
Given that there are no reported studies on the switching between oxidative Heck and conjugate addition reactions using Pd(II), the discovery that the selectivity of the reaction switches when the solvent is changed prompted the group to investigate this switch further and examine the factors which influence the formation of one product over another (Scheme 55).



Scheme 55: Project aim – to investigate the switching between oxidative Heck and conjugate addition reactions

2.3 Previous work in the Lee group

As previously mentioned in section 2.2, the solvent screen conducted during the work in the Lee group on conjugate addition reactions indicated that more polar solvents favoured the oxidative Heck product over the conjugate addition product in the Pd(II) catalysed reaction between cyclic enones and aryl boroxines.[24] The catalyst used for the solvent screen was generated *in situ* using $Pd(OAc)_2$ and triflic acid. 2-Cyclohexen-1-one **37** was chosen as the substrate and tris(*p*-methoxyphenyl)boroxine **6c** as the coupling partner given that these reagents together had given good results in previous work. Results from the screen are shown below (Table 1).



37 + **6c**[a] → **84c** + **38c**

Entry	Solvent	Yield 84c (%)[b]	Yield 38c (%)[b]
1	$ClCH_2CH_2Cl$	94[c]	-
2	$ClCH_2CH_2Cl$ + DMF (4 equiv.)	79[c]	20[c]
3	DMF	-	trace
4	Acetone	-	14
5	MeCN	trace	trace
6	Dimethyl acetamide	trace	trace
7	MeOH	-	4
8	*N*-methylpyrrolidinone	12	4
9	DMSO	-	33[c]
10[d]	DMSO	-	84[c]

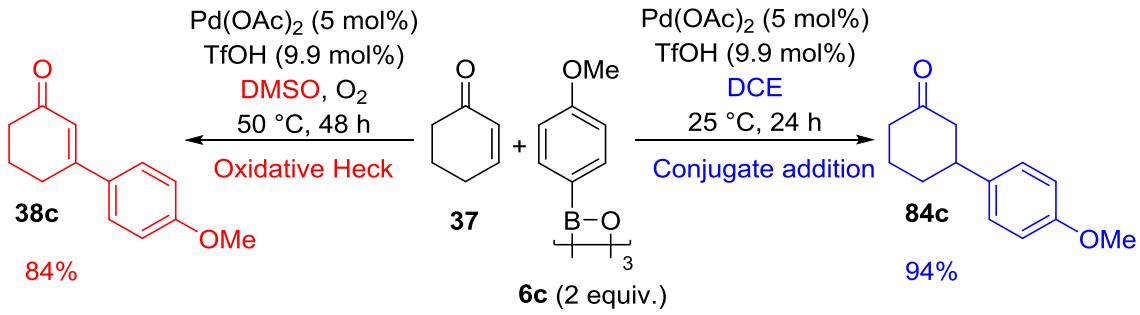
[a]Commercial aryl boronic acid was heated under vacuum to generate boroxine. [b]Determined by ^1H NMR analysis of crude mixture, unless otherwise stated. [c]Isolated yield. [d]50 °C, 48 h

Table 1: Solvent screen for the reaction between 2-cyclohexen-1-one and tris(*p*-methoxyphenyl)boroxine

When more polar solvents were used, it became apparent that there was a tendency to form oxidative Heck product **38c**. However, conversions remained poor with the

exception being when DMSO was used as the solvent. DMSO was found to form the oxidative Heck product **38c** exclusively in 33% conversion at room temperature (Entry 9). Pleasingly, warming the reaction to 50 °C and increasing the reaction time improved the conversion considerably and 84% isolated yield of oxidative Heck product was obtained (Entry 10).

This promising result, coupled with formation of the conjugate addition product **84c** in 94% yield when dichloroethane was used as the solvent (Table 1, Entry 1), formed the basis of this project (Scheme 56).



Scheme 56: Initial results demonstrating switching between oxidative Heck and conjugate addition reactions by switching solvent*

The initial result for formation of the oxidative Heck product **38c** exclusively when DMSO was used as the solvent (Table 1, Entry 10) was the starting point for further optimisation of the oxidative Heck reaction.

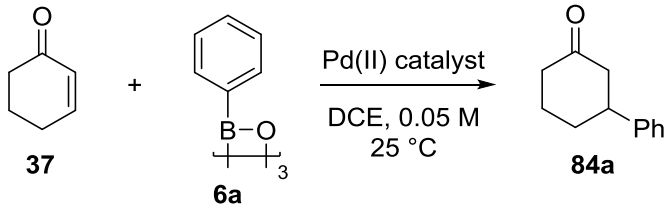
The aim of the project was to firstly investigate this switching further by optimising the reaction conditions. Once optimisation had been completed, substrate and boronic acid screens would be carried out using optimised conditions for both the oxidative Heck and conjugate addition reactions. Additionally, it was hoped that during the course of our investigations we would be able to shed some light on possible reasons for the switching between reaction outcomes when different solvents are used.

2.4 Conjugate addition reaction

*Work carried out by Steven Levey, MChem project student

2.4.1 Optimisation of reaction conditions

Our first investigations into optimisation of the conjugate addition reaction conditions focussed on establishing whether the premade catalyst [$Pd(MeCN)_4(OTf)_2$] or the *in situ* generated catalyst [$Pd(OTf)_2$] would be best for our studies. Both had been utilised and found to be effective in the aforementioned conjugate addition work in the Lee group[24] yet it was important to establish which would be more suited to this project. A screen of both catalysts was carried out using 2-cyclohexen-1-one **37** as the substrate and triphenyl boroxine **6a** as the boronic acid coupling partner. Previous work into conjugate addition reactions had found that using aryl boroxines (the dehydrated trimer of the corresponding boronic acid) rather than aryl boronic acids was vital for good conversion. Additionally, given that sodium nitrate had been a useful additive in previous conjugate addition work by reducing the formation of the phenol of the boroxine and also the homo-coupled product,[24] the effect of sodium nitrate on conversion was also investigated by varying the number of equivalents used.



37 **6a** **84a**

***In situ* catalyst:** $Pd(OAc)_2$ (5 mol%), TfOH (9.9 mol%)
Premade catalyst: $Pd(MeCN)_4(OTf)_2$ (5 mol%)

Entry	Boroxine 6a:[a] Substrate 37	Catalyst	Equiv. $NaNO_3$	Time (h)	Yield
1	2:1	*In situ*	0	18	33% conv.
2	2:1	*In situ*	1	40	33% conv.
3	2:1	Premade	1	42	69%[b]
4	3:1	Premade	2	40	77%[b]

[a]Equivalents of single aryl group used in the reaction rather than trimer. [b]Isolated yield

Table 2: Initial optimisation reactions

Firstly, reactions with the *in situ* catalyst were carried out; one in the absence of sodium nitrate and another with 1 equivalent of the additive. Conversions were poor for both reactions (Table 2, Entries 1 and 2) and even leaving the reaction for longer did not increase conversion (Entry 2). Conversions were calculated by examining the amount

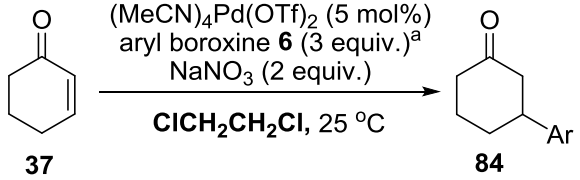
of starting material remaining in the reaction mixture by ^{1}H NMR. However, during later optimisation studies for the oxidative Heck reaction, it became apparent that the volatility of 2-cyclohexen-1-one was affecting conversion calculations. In this case, the volatility of 2-cyclohexen-1-one would actually cause the conversion to be lower than reported for Entries 1 and 2 (Table 2) and therefore it can still be assumed that the *in situ* generated catalyst performs poorly with the above reaction conditions.

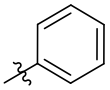
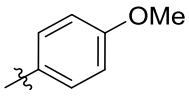
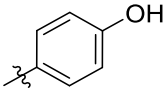
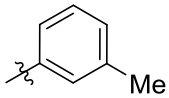
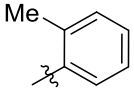
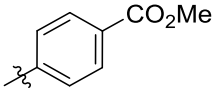
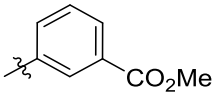
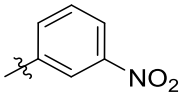
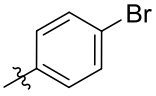
Next, our attention turned to examining the premade catalyst. Given that sodium nitrate did not seem to have a detrimental effect on yield in reactions using the *in situ* catalyst, and knowing that it can help to prevent homocoupling of the boronic acid, we decided to carry out screening of the premade catalyst with sodium nitrate. Using 1 equivalent of sodium nitrate and the premade catalyst in the above reaction gave an isolated yield of 69% (Entry 3). Increasing the equivalents of boroxine **6a**, and also sodium nitrate increased the yield of **84a** to 77% (Entry 4) which was a very promising result.

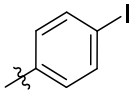
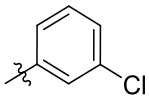
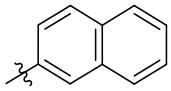
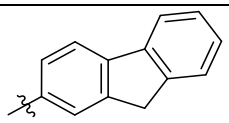
Despite our best result to date being a 94% yield with the *in situ* formed catalyst ($Pd(OTf)_2$ generated from $Pd(OAc)_2$ and triflic acid) and tris(*p*-methoxyphenyl)boroxine, previous studies have shown that this particular boroxine is very reactive. Therefore it was prudent to conduct optimisation work using a less reactive boroxine (such as triphenyl boroxine) in order for the optimised reaction conditions to be appropriate for a wide range of boroxines with different electronic and steric properties.

2.4.2 Conjugate addition reaction – boroxine screen

Having optimised the conjugate addition reaction conditions and found that the premade catalyst [$Pd(MeCN)_4(OTf)_2$] gives the best result with 3 equivalents of boroxine **6a** (note: actually 1 equivalent of the boroxine trimer but 3 equivalents of the single aryl group of the trimer) and 2 equivalents of sodium nitrate, a boroxine screen was carried out (Table 3). Reactions were monitored by TLC and reaction times varied depending on the boroxine used.



Entry	Aryl	Time (h)	Isolated yield (%)
1	**6a** 	40	**84a** 77
2	**6c** 	24	**84c** 74
3	**6d** 	24	**84d** 67
4	**6e** 	42	**84e** 68
5	**6f** 	42	**84f** 76
6	**6g** 	20	**84g** 72
7*	**6h** 	17	**84h** 75
8	**6i** 	66	**84i** 59
9	**6j** 	23	**84j** 44 O_2 atmosphere - 71

10	**6k** 	20	**84k** 42 O_2 atmosphere - 32
11*	**6l** 	23	**84l** 82
12*	**6m** 	17	**84m** 84
13*	**6n** 	23	**84n** 51

[a]Commercial boronic acid was heated under vacuum to generate boroxine. Equiv. refers to the equivalents of boronic acid, or single aryl group of the boroxine trimer.

Table 3: Conjugate addition reaction boroxine screen[*]

The boroxine screen showed that the reaction is tolerant of a range of boroxines bearing groups with differing steric and electronic properties and substitution at *ortho-*, *meta-* and *para-* positions on the aryl ring. Electron-rich boroxines (**6a, 6c-f**) give good to excellent yields (Table 3, Entries 1 to 5). The yields generally decrease somewhat when electron-withdrawing boroxines are used (**6g-i** and **6l**, Entries 6, 7, 8, 11) which may be caused by higher propensity of electron-withdrawing boroxines to form the homocoupled aryl dimers compared to their electron-donating counterparts. Pleasingly, oxidisable tris(2-fluorenyl)boroxine (**6n**) gives a moderate yield (Entry 13) and tris(2-naphthyl)boroxine (**6m**) performs well under our conditions (Entry 12).

Tris(*p*-bromophenyl)boroxine and tris(*p*-iodophenyl)boroxine (**6j** and **6k**) gave poor yields with the optimised reaction conditions (Entries 9 and 10), presumably due to the tendency for palladium(0) to insert into carbon-halogen bonds. Given that palladium(0) is not formed during conjugate addition reactions, its formation in this instance could arise from homocoupling of the boronic acid. Both these reactions were repeated under an oxygen atmosphere to reoxidise any palladium(0) to palladium(II). Whilst this unfortunately did not increase the yield when tris(*p*-iodophenyl)boroxine (**6k**) was used (42% to 32%, Entry 10), pleasingly the yield of **84j** increased significantly from 44% to

[*]The boroxine screen was carried out primarily by the author. However, Dr Pauline Glen and Julian Boehnke assisted in the latter stages of the screen and their results are indicated by an asterisk (*).

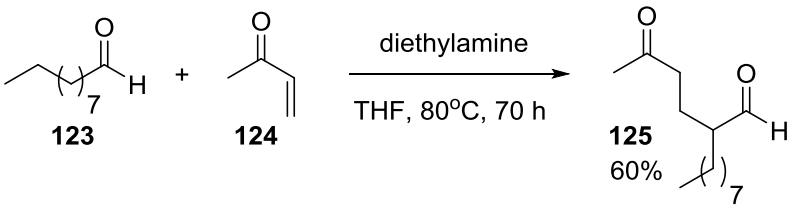
71%. The bromo functionality provides a handle for further functionalisation, for instance *via* Pd(0) cross-coupling reactions.

2.4.3 Conjugate addition reaction – substrate screen

Having successfully screened a range of aryl boroxines, our attention next turned to investigating alkene substrate scope in the conjugate addition reaction. The author's contribution to this part of the project mainly focussed on optimisation work for electron-rich substrates in addition to substrate synthesis where necessary. As previously mentioned, various members of the Lee group contributed to this project and a large proportion of the substrate screen was carried out by other students. However, all the results obtained by both the author and other members of the Lee group are shown for completeness (Table 6).

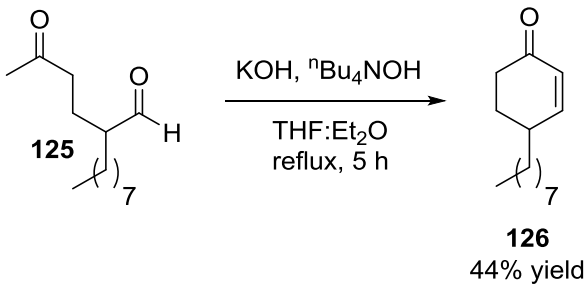
Substrate synthesis

The cyclic alkene substrates required for the substrate screen were either commercially available or synthesised by oxidation of the cycloalkane precursor or *via* Robinson annulations. For instance, using a known synthetic route published by Hagiwara *et al.*,[26] a Michael addition was carried out with decanal **123** and methyl vinyl ketone **124** using diethylamine as the base (Scheme 57) to give the precursor **125** in reasonable (60%) yield.



Scheme 57: Synthesis of 2-(3-oxobutyl)decanal

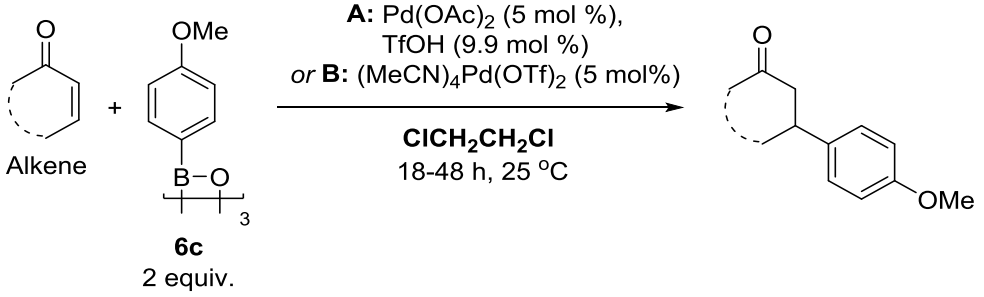
A Robinson annulation of the substrate precursor **125** was then carried out using potassium hydroxide and ^{n}butyl ammonium hydroxide to form the desired product **126** in moderate yield (Scheme 58, 44%).*



Scheme 58: Synthesis of 4-octylcyclohex-2-en-1-one

2.4.4 Conjugate addition alkene substrate screen optimisation

Similar reaction conditions to the boroxine screen were adopted for the alkene substrate screen. However, previous optimisation in the group had established that using 2 equivalents of the boroxine were optimal and sufficient to give good yields. Additionally, earlier studies had indicated that the *in situ* catalyst (generated from $Pd(OAc)_2$ and TfOH) performed better with more sterically hindered substrates, and the premade catalyst $Pd(MeCN)_4(OTf)_2$ was more suited to more electron-rich systems. With this in mind, the substrate screen was carried out using the most appropriate catalyst for each individual substrate (Scheme 59). Reactions were monitored by TLC analysis and took between 18 and 48 hours to reach completion.

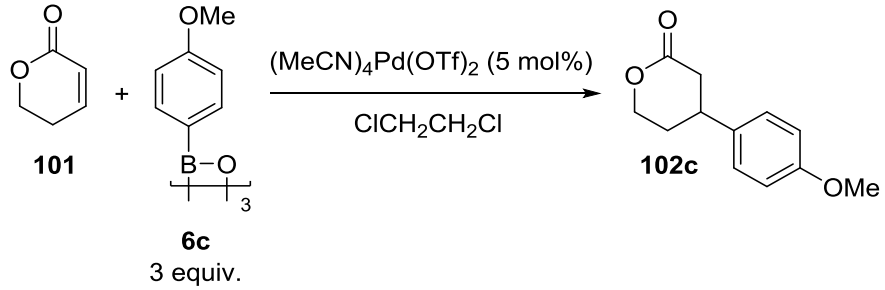


Scheme 59: Reaction conditions used for conjugate addition substrate screen

*The remaining substrates shown in Table 6 which were not commercially available were synthesised by other members of the Lee Group.

For cyclohexenone substrates **37, 129, 130** and **126** (see Table 6), the optimised reaction conditions (conditions A) were found to give good yields. However, turning our attention to relatively more electron-rich substrates such as **101**, the yields reduced somewhat and further optimisation was deemed necessary.

Using 5,6-dihydro-2*H*-pyran-2-one **101** as the substrate and increasing the equivalents of boroxine **6c** to three, a number of reactions were carried out using different reaction times, temperatures and equivalents of sodium nitrate. The standard reaction conditions used for the substrate screen (25 °C, no sodium nitrate) gave a conversion of 70% using dibenzyl ether as the internal standard (Table 4, Entry 1) and therefore we wanted to investigate if this could be increased. Adding 2 equivalents of sodium nitrate did not show any improvement to conversion (Entry 2). Warming the reaction mixture to 30 °C and leaving the reaction for 48 hours actually saw a reduction in conversion (Entry 3). However, on using these conditions and adding sodium nitrate to the reaction mixture, the conversion increased, giving the best conversion of all the conditions screened (76%, Entry 4) and an isolated yield of 68% product **102c**.



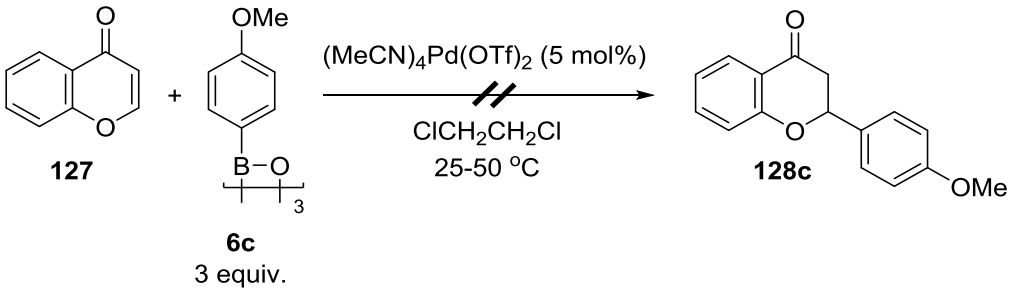
Entry	Temp. (°C)	Equiv. $NaNO_3$	Time (h)	% conv. to 102c[a]
1	25	0	23	70
2	25	2	23	69
3	30	0	48	61
4	30	2	48	76 (isolated yield 68%)

[a]Determined by ^{1}H NMR analysis using dibenzyl ether as internal standard.

Table 4: Optimisation of reaction conditions for substrate **102c**

Another substrate included in the substrate screen was chromone **127** (Table 5). Given that we expected this substrate to also be challenging due to its more electron-rich nature (relative to **37**), 3 equivalents of boroxine were used. Two reactions were carried out, with 0 and 2 equivalents of sodium nitrate (Table 5). Monitoring by TLC analysis indicated no product formation even after two days. The reactions were then warmed to 50 °C to hopefully induce product formation yet even after a further 5 days, there was

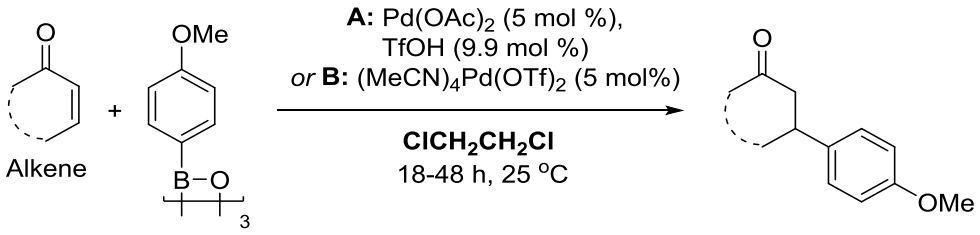
still no evidence of product. A possible reason for this is that the substrate is too electron-rich for our reaction conditions.

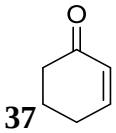
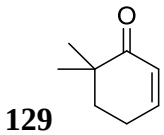
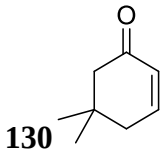
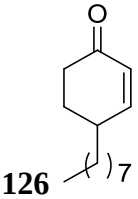
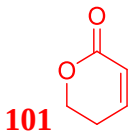
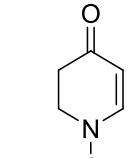
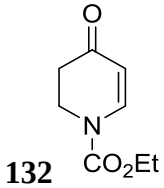
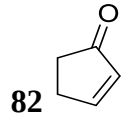


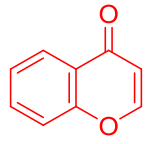
Entry	Equiv. $NaNO_3$	Time (h)	% conv. to 128c
1	0	48	0
2	2	48	0

Table 5: Conjugate addition on chromone as the substrate

With these results in hand, a substrate screen was completed and for more electron-rich substrates the conditions found to be suitable for 5,6-dihydro-2*H*-pyran-2-one conditions were used (Table 6).



Entry	Substrate	Catalyst	Equiv. boroxine	Time (h)	Isolated yield (%)
1	 **37**	A	2	24	**84c** 94%
2	 **129**	A	2	24	**133c** 76%
3	 **130**	A	2	24	**134c** 75%
4[c]	 **126**	A	2	18	**135c** 94% 8:1 dr
5[a,b]	 **101**	B	3	48	**102c** 68%
6[a]	 **131**	B	3	24	**136c** 88%
7[a]	 **132**	B	3	48	**137c** 60%
8	 **82**	A	2	24	**83c** 61%

9[a]	 **127**	B	3	7 days 25-50°C	No reaction

[a]2 equiv. $NaNO_3$ added. [b]30 °C. [c]1 equiv. $NaNO_3$ added; author's work shown in red.

Table 6: Conjugate addition reaction substrate screen

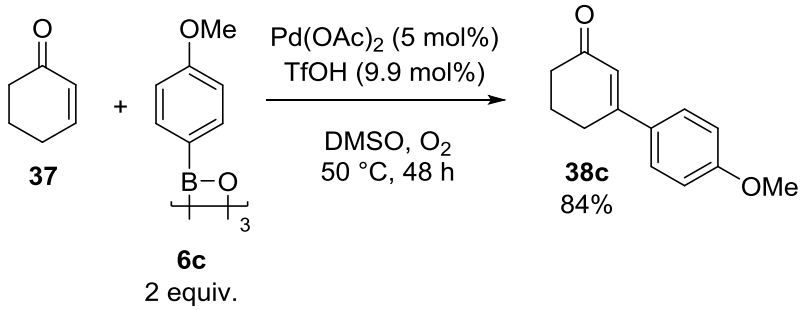
The substrate screen demonstrated the versatility of the reaction conditions to a range of different substrates. Substrates bearing alkyl groups at different positions on the cyclohexenone ring (**37, 129** and **130,** Table 6, Entries 1-3) performed well with the *in situ* generated catalyst (conditions A) and gave very good to excellent yields. Even an alkyl chain at the γ position close to the reactive alkene centre (**126,** Entry 4) gave an excellent yield, with good diastereomeric ratio.

As previously discussed, after further optimisation more electron-rich substrates gave good to excellent yields of the conjugate addition product using conditions B (**101, 131** and **132,** Entries 5-7) with the exception of chromone (**127,** Entry 9). Additionally, reducing the ring size and using 2-cyclopenten-1-one **82** as the substrate also formed the conjugate addition product in good 61% yield (Entry 8).

2.5 Oxidative Heck reaction

2.5.1 Reaction optimisation

Following on from the initial promising result for the oxidative Heck reaction carried out by Steven Levey (Scheme 60), our attention next turned to the oxidative Heck reaction on cyclic enones with aryl boronic acids.



Scheme 60: Initial oxidative Heck result by Steven Levey

Initial optimisation work on the oxidative Heck reaction building on Steven Levey's result (Scheme 60) was unfortunately hampered by irreproducible results and poor yields. Part of the reason for this was attributed to the volatility of 2-cyclohexen-1-one and conversions calculated from ^{1}H NMR analysis based on the remaining starting material in the reaction as a reference were deemed to be unreliable and conversions misleading. Therefore, these results are not included in this chapter, although some useful knowledge was gained from these initial studies with regards to suitable reaction conditions. Once the reasons for the unreliability of results had become clear, conversions or yields for all further reactions were calculated either using an internal standard (dibenzyl ether or 4-nitrobenzaldehyde), or by isolating the product.

Despite this setback, our initial studies did enable us to establish some reasonable reaction conditions for the oxidative Heck reaction which we could then optimise further.

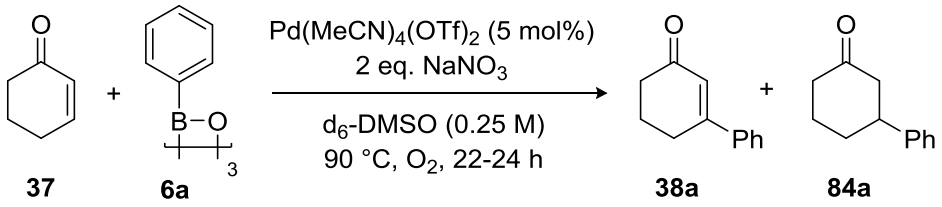
The initial catalyst loading of 5 mol% used in the original solvent screen (Table 1), was deemed appropriate for optimisation work. For optimisation, the premade catalyst $Pd(MeCN)_4(OTf)_2$ was used. In initial studies, it was found to be as effective as the *in situ* generated catalyst and therefore it was decided that for ease of handling (avoiding

the need to use triflic acid) this catalyst was used for optimisation work. Also, in the initial solvent screen (Table 1), molecular oxygen was used as the chosen oxidant and therefore used for optimisation studies. In order to monitor reactions easily by NMR, d_6-DMSO was used as the solvent at a concentration of 0.25 M.

As previously mentioned, prior investigations in the group had found that using sodium nitrate as an additive tends to reduce the formation of both the boronic acid dimer, and also the phenol derived from the boronic acid. Therefore, optimisation was carried out using 2 equivalents of this additive.

Our initial optimisation work, despite being hampered by irreproducible results and poor yields, had indicated that a higher temperature than 50 °C used in the initial solvent screen was perhaps needed to give a good conversion to oxidative Heck product. Therefore, we used a temperature of 90 °C to first conduct a screen to examine what effect changing the stoichiometry of substrate and boroxine would have on conversion (Table 7).

We examined a variety of stoichiometries of substrate to boroxine, using 2-cyclohexen-1-one **37** as the substrate and triphenylboroxine **6a** as the coupling partner (Table 7).



37 **6a** **38a** **84a**

Entry	Equiv. 37	Equiv. 6a	% conv. to 38a[a]	% conv. to 84a[a]
1	1	3	22	0
2	1	2	13	0
3	1	1	6	0
4	2	1	9	0
5	3	1	22	0
6	4	1	35	0
7	5	1	33	0

[a]Determined by ^{1}H NMR analysis using dibenzyl ether as internal standard.

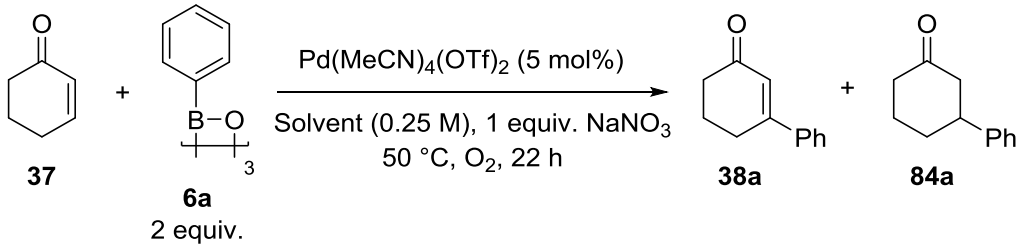
Table 7: Optimisation of reaction stoichiometry

Unfortunately, none of the reactions carried out gave good conversion to the oxidative Heck product **38a**. However, no evidence of conjugate addition product **84a** was seen for any of the reactions and the oxidative Heck product **38a** was formed exclusively. Conversions were similar for both 3:1 boroxine **6a** to substrate **37** and also using the reverse stoichiometry of 1:3 boroxine to substrate (Entries 1 and 5). The conversions increased to over 30% when 4 and 5 equivalents of substrate were used but were still poor (Entries 6 and 7).

From these results we decided to use a stoichiometry of 1 equivalent substrate to 3 equivalents of boroxine (3 equivalents of the single aryl group of the boroxine trimer) for further optimisation studies. Although using an excess of substrate (4 or 5 equivalents, Entries 6 and 7, Table 7) does give a higher conversion, we decided that it was prudent to use the boronic acid as the excess reagent given the tendencies for boronic acids to homocouple which would obviously reduce yield considerably if the boronic acid were to be the limiting reagent.

Oxidative Heck reaction optimisation – solvent screen

Despite attempted further optimisation of the oxidative Heck reaction, conversions were still not comparable to the initial result obtained when DMSO was used as a solvent (84% yield, Table 1, Entry 10 note: however this result did use the more active aryl boroxine **6c** and the *in situ* generated catalyst). Therefore, optimisation studies were continued with another solvent screen. For practical reasons, the temperature was lowered from previous optimisation work (see Table 7) to 50 °C and a range of solvents investigated, examining the ratio of oxidative Heck to conjugate addition product as well as the conversion (Table 8). Additionally, it was decided that for this screen the amount of sodium nitrate used as an additive would be reduced to 1 equivalent and a stoichiometry of 2:1 boroxine **6a** (aryl group of the boroxine trimer) to substrate **37** would be used.



37 **6a** 2 equiv. **38a** **84a**

Entry	Solvent	% conv. to 38a[a]	% conv. to 84a[a]
1	d_6-DMSO	68	23
2	DMF	Could not calculate	
3	NMP	0	0
4	Acetone	14	86
5	Methanol	6	60
6	Acetonitrile	21	79

[a]Determined by ^{1}H NMR analysis*

Table 8: Oxidative Heck reaction optimisation solvent screen

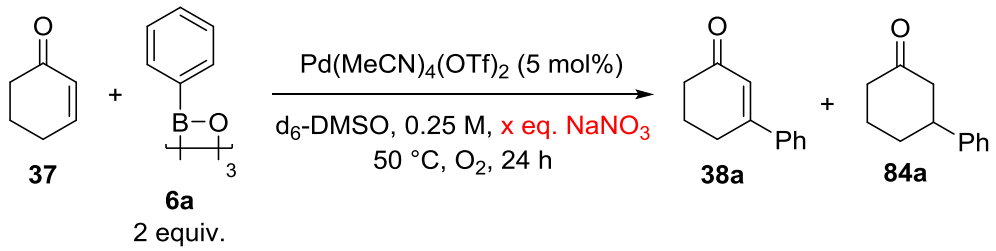
Despite the poor conversions to date in optimisation studies, the solvent screen confirmed that DMSO was the best solvent in terms of yield of oxidative Heck product **38a** and for selectivity over the conjugate addition product **84a** (Entry 1, Table 8).

*No internal standard was used in the solvent screen. Therefore the ratios of conjugate addition to oxidative Heck products are accurate but the overall conversions may include some degree of error given that overall conversions are based on the amount of 2-cyclohexen-1-one **37** left in the reaction after 22 hours.

Unfortunately some conjugate addition product was still formed but a conversion of 68% to oxidative Heck product using a lower temperature of 50 °C (compared to 90 °C used in Table 1) certainly indicated progress in the optimisation studies.

Oxidative Heck reaction optimisation – investigating the equivalents of sodium nitrate

Given that 50 °C and DMSO were established as the best temperature and solvent for the reaction, our attention turned to examining the equivalents of sodium nitrate used in the reaction. Using a stoichiometry of 2:1 boroxine **6a** to substrate **37**, and the conditions shown below, reactions were carried out using 0, 1 and 2 equivalents of sodium nitrate to see what effect the additive would have on conversion (Table 9).



Entry	Equiv. $NaNO_3$	% conv. to 38a[a]	% conv. to 84a[a]
1	0	57	13
2	1	50	14
3	2	53	16

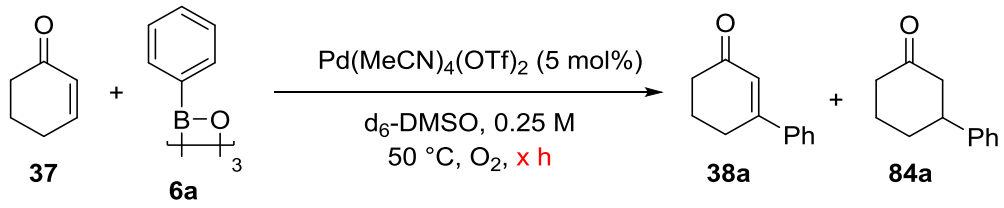
[a]Determined by ^{1}H NMR analysis using dibenzyl ether as internal standard.

Table 9: Optimising the equivalents of sodium nitrate

Despite previous investigations in the group indicating that sodium nitrate improved yield by suppressing homocoupling,[24] this screen showed that within error, the use of sodium nitrate in the reaction does not make much of a difference to conversions to oxidative Heck product **38a**. Therefore, sodium nitrate was omitted from further optimisation reactions.

Following this result we decided that it would be sensible to reoptimise the equivalents of boronic acid given that our original screen investigating stoichiometries used 2 equivalents of sodium nitrate and this may well have affected results (Table 7).

Oxidative Heck reaction optimisation – investigating the stoichiometry of substrate and boroxine



Entry	Equiv. 6a	Time (h)	% conv. to 38a[a]	% conv. to 84a[a]
1	2	47	62	24
2	3	47	29	17
3	1.5	22	47	24
4	2	22	59	20
5	2.5	22	44	24

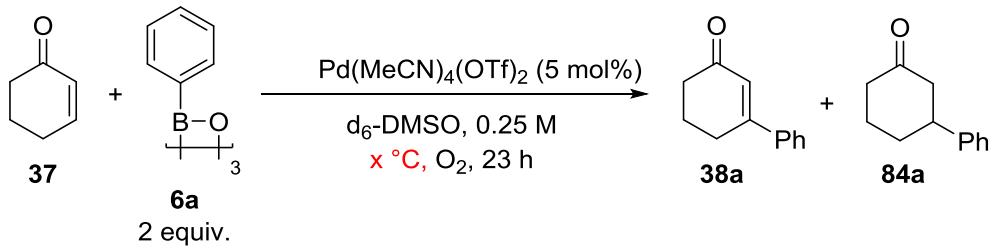
[a]Determined by ^{1}H NMR analysis using 4-nitrobenzaldehyde as internal standard.

Table 10: Investigating the reaction stoichiometry and reaction time with 0 equivalents sodium nitrate

Initial reactions (Table 10, Entries 1 and 2), indicated that 2 equivalents gave the best conversion to oxidative Heck product **38a** and interestingly, increasing the equivalents resulted in a considerable drop in conversion. These reactions were conducted over two days in an effort to increase conversion. Taking the best result (Entry 1), the reaction time was reduced and further reaction stoichiometries were investigated; 1.5, 2 and 2.5 equivalents of boroxine, over 22 hours. Again, 2 equivalents of boroxine not only gave the best conversion to oxidative Heck product **38a** but also the lowest conversion to conjugate addition product **84a** (Entry 4).

Oxidative Heck reaction optimisation – temperature screen

Following on from investigating optimal stoichiometry (Table 10), an increase in conversion was still desirable and therefore different temperatures were investigated to see if this would make a difference (Table 11). Given that the conversion to oxidative Heck product **38a** was comparable when 2 equivalents of boroxine were used over a reaction time of both 47 and 22 hours (Table 10, Entries 1 and 4), it was decided that a reaction time of one day would be used for the temperature screen (Table 11).



Entry	Temp. (°C)	% conv. to 38a[a]	% conv. to 84a[a]
Table 10, Entry 4	50	59	20
2	70	26	0
3	30	25	9

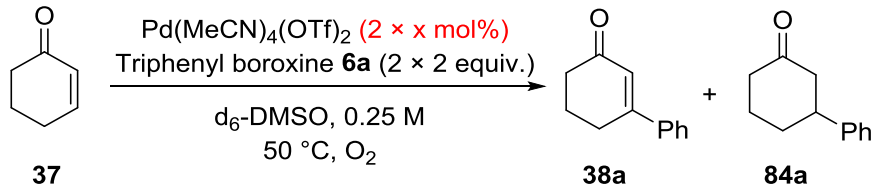
[a]Determined by ^{1}H NMR analysis using 4-nitrobenzaldehyde as internal standard.

Table 11: Temperature screen

The temperature screen showed that both an increase and decrease in temperature from 50 °C caused a drop in conversion to oxidative Heck product. Therefore, it was decided that 50 °C would be the optimal reaction temperature to use for further optimisation work.

Oxidative Heck reaction optimisation – portionwise addition of catalyst and boroxine

Given that conversions still remained moderate in our optimisation work and needed improvement, investigation of catalyst loading and portionwise addition of catalyst and boronic acid was finally investigated. Obviously it would be desirable to carry out the reaction with minimal catalyst loading but given the difficulties experienced in trying to increase conversions we decided to also investigate an increase in catalyst loading to see if this would have a positive effect on conversions (Table 12).



Entry	Portion 1	Portion 2			Reaction time	% conv.[b]	
	mol% catalyst	Added at x h	mol% catalyst	Equiv. 6a		38a	84a
1[a]	5	N/A	N/A	N/A	47	62	24
2	6	19	5	2	41	70	23
3	3	19	3	2	41	30	30
4	11	N/A	N/A	N/A	41	55	0
5	5	8.5	5	2	24	62	25

[a]Table 10, Entry 1. [b]Determined by ^{1}H NMR analysis using 4-nitrobenzaldehyde as internal standard.

Table 12: Portionwise addition of catalyst and boroxine

Various combinations of catalyst loading, the number of portions of catalyst and boroxine **6a** added in addition to reaction time were investigated and compared to the best result to date which gave 62% conversion to oxidative Heck product **38a** and 24% conversion to conjugate addition product **84a** (Table 10, Entry 1). This result is included in Table 12 (Entry 1) for ease of comparison.

Firstly, a portionwise addition approach of catalyst and boroxine was adopted and an additional 5 mol% catalyst and 2 equivalents of triphenyl boroxine **6a** were added to the reaction mixture after 19 h (Entry 2). Pleasingly, whilst conversion to conjugate addition product **84a** remained the same as when only one portion of 5 mol% catalyst was added (Entry 2 *versus* Entry 1), the conversion to oxidative Heck product **38a**

increased to 70%. This result clearly indicated that additional catalyst and boroxine added part way through the reaction certainly helped to increase conversion. Using this portionwise addition approach we then investigated if the catalyst loading could be reduced by adding 3 mol% catalyst at the beginning of the reaction and a further portion of 3 mol% catalyst and 2 equivalents boroxine after 19 hours (Entry 3). This unfortunately did not give comparable conversions and also the ratio of oxidative Heck to conjugate addition product became 1:1 indicating that a higher catalyst loading was necessary.

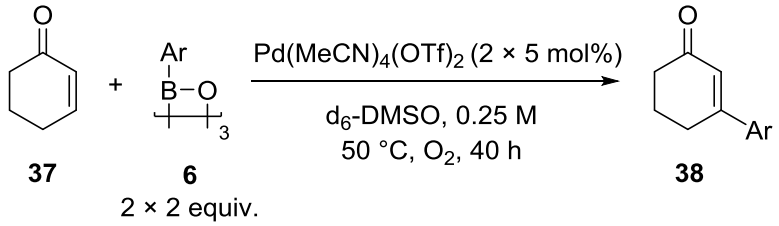
Next, given that our best result to date was using 2 portions of 5 mol% catalyst (Entry 2), we then investigated using a higher catalyst loading at the beginning of the reaction (in this case, 11 mol%, Entry 4) to see if adding 10 mol% catalyst over 2 portions rather than 1 was strictly necessary. The conversion to oxidative Heck product **38a** did in fact reduce to 55%, compared to 70% when the portionwise addition method was adopted (Entry 4 *versus* Entry 2). Interestingly, no conjugate addition product **84a** was formed in this reaction. Despite the formation of oxidative Heck product exclusively, it was decided that the portionwise addition method which gave the best conversion to oxidative Heck product would be the best method to pursue.

The final reaction in this study was to investigate whether a drop in reaction time from two days to one day would affect the conversion. Using the portionwise addition method, and adding the additional portions of catalyst and boroxine after 8.5 hours reduced the yield of oxidative Heck product **38a** to 62%, although the conversion to conjugate addition product **84a** was comparable to the 2 day reaction (Entry 5 *versus* Entry 1).

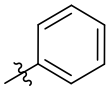
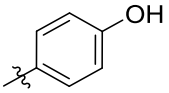
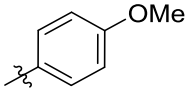
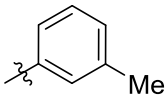
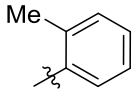
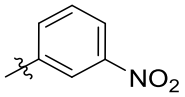
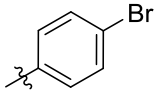
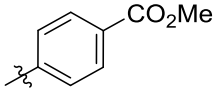
From these optimisation reactions, the best conditions were found to be portionwise addition of catalyst, where two portions of catalyst (5 mol%) were added; one at the start of the reaction and the second after 19 hours (Table 12, Entry 2). The reaction was then left for another 21 hours before work up and purification of the product. These conditions were then used for a boroxine screen.

2.5.2 Oxidative Heck reaction – boroxine screen

Using the best reaction conditions from our optimisation work (Table 12, Entry 2), a range of boroxines were screened with differing steric and electronic properties (Table 13).



37 **6** 2 × 2 equiv. **38**

Entry	Aryl	Isolated yield (%)
1	**6a** 	**38a** 68
2	**6d** 	**38d** 60
3	**6c** 	**38c** 58
4	**6e** 	**38e** 46
5	**6f** 	**38f** 47
6	**6i** 	**38i** ~50% conv.[a]
7[b]	**6j** 	**38j** Complex mixture of products
8	**6g** 	**38g** 60% conv.[c]

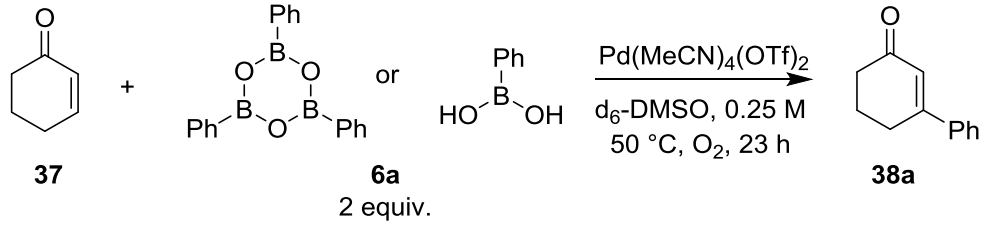
[a]Large amount of dimer formed. Conversion calculated according to remaining starting material as internal standard coelutes with product so could not be used. [b]O_2 atmosphere. [c]Determined by ^{1}H NMR analysis using dibenzyl ether as internal standard.

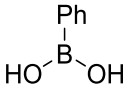
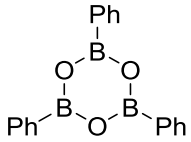
Table 13: Oxidative Heck reaction initial boroxine screen

This screen gave good results with a number of boroxines and despite the conjugate addition product being present in the catalyst loading studies shown in Table 12, for this screen no conjugate addition product formation was evident (except for Entry 1 which is the oxidative Heck product isolated from Entry 2, Table 12), demonstrating full switching to oxidative Heck product **38**. Yields were moderate however, in comparison to the less challenging conjugate addition reaction. With some of the oxidative Heck reactions being hampered by poor conversions and low yields (Table 13, Entries 4-8), we thought that it may be useful to investigate how the yields are affected when the boronic acid is used in the reaction, rather than the boroxine. Whilst previous studies had indicated that the boroxine trimer of the corresponding boronic acid was necessary for conjugate addition reactions, this had not been investigated with regards to our work on oxidative Heck reactions.

Oxidative Heck boronic acid screen – comparison between boronic acid and boroxine

In order to investigate whether using the boroxine or boronic acid in the oxidative Heck reactions gave different results, we carried out two reactions; one with boronic acid (recrystallised from water) and the second with boroxine (formed by taking the commercial boronic acid and heating under vacuum). The reactions were run over 24 hours using triphenyl boroxine/phenyl boronic acid as the coupling partner (Table 14). A ratio of 1:2 substrate **37** to boronic acid **6a** was used, which for the boroxine equated to 0.66 equivalents of the trimer (i.e. 2 equivalents of the single aryl group of the boroxine).

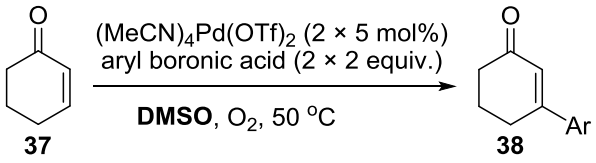


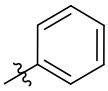
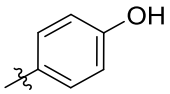
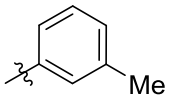
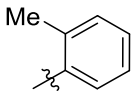
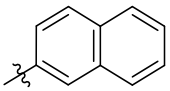
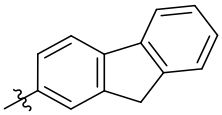
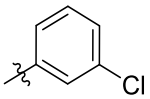
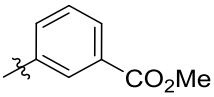
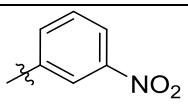
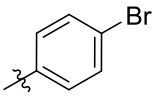
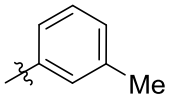
Entry	Boronic acid/boroxine	% conv.[a]
1		64
2		48

[a]Determined by ^{1}H NMR analysis using dibenzyl ether as internal standard.

Table 14: Comparison of aryl boroxine to aryl boronic acid in the oxidative Heck reaction

Interestingly, when boronic acid was used in the reaction, the conversion was considerably higher than when boroxine was used. Using this result, we then decided to repeat the oxidative Heck reactions which had given poor conversions and low yields in order to see if the yields could be improved when boronic acid (recrystallised from water) was used as the coupling partner (Table 15).



Entry	Aryl	Isolated yield (%) using boroxine	Isolated yield (%) using boronic acid
1	**6a** 	**38a** 68	**38a** 59
2	**6d** 	**38d** 60	-
3	**6e** 	**38e** 46	**38e** 66
4	**6f** 	**38f** 47	**38f** 57
5	**6m** 	-	**38m** 68
6	**6n** 	-	**38n** 48[a]
7	**6l** 	-	**38l** 53[b]
8	**6h** 	-	**38h** 43[b]
9	**6i** 	**38i** 50% conv.	**38i** 50% conv.[b]
10	**6j** 	Complex mixture of products	**38j** 24[b,c,d]
11	**6e** 	-	**38e** 66[d,e]

[a]34% conjugate addition product isolated. [b]Three portions of 5 mol% catalyst. [c]1.5 equiv. benzoquinone used. [d]Some conjugate addition product evident in the reaction but not quantified. [e]Commercial aryl boronic acid + water (1.5 equiv.).

Table 15: Oxidative Heck reaction – boronic acid screen[*]

[*]Additional members of the Lee group also worked on this screen, mainly undergraduate ERASMUS student Julian Boehnke; results attributed to the author are shown in red in Table 15.

Generally, an improvement in yield was seen when aryl boronic acids were used rather than aryl boroxines (Entries 3 and 4). Despite phenyl boronic acid giving a slightly lower yield of oxidative Heck product than when the corresponding boroxine was used (Entry 1), it was decided that boronic acids rather than boroxines would be used to complete this screen.

The boronic acid screen shows that a range of boronic acids are tolerated in the reaction and moderate to good yields of oxidative Heck product can be obtained. Aryl boronic acids bearing substituents at the *ortho-*, *meta- and para-* positions and polyaromatics (**6a, d, e, f** and **m**) give the desired oxidative Heck product using our optimised reaction conditions (Entries 1-5). Readily oxidisable 2-fluorene boronic acid **6n** also tolerates the reaction conditions and gives a moderate yield of oxidative Heck product **38n** (Entry 6), although 34% conjugate addition product was also isolated in this case.

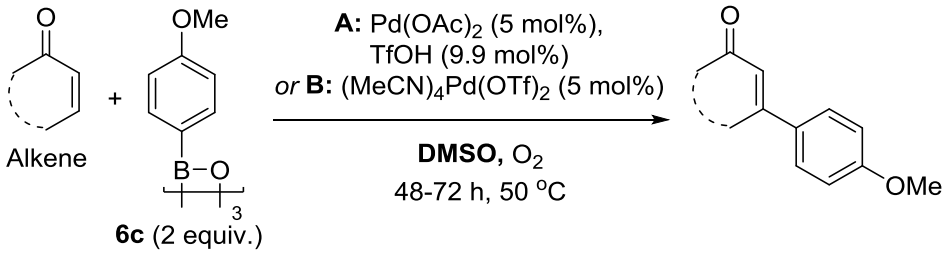
For a number of electron-poor boronic acids (**6h, i, j** and **l**) which are known to be challenging coupling partners, a third portion of catalyst was needed in order to push the reaction to completion or give a decent yield (Entries 7-10). Additionally, *p*-bromophenyl boronic acid **6j** proved to be challenging, presumably for the same reasons as specified in the conjugate addition work; the propensity for palladium(0) to insert into C-Br bonds. By adding benzoquinone as an additional oxidant, a yield of 24% oxidative Heck product **38j** was obtained with a small quantity of conjugate addition product. Despite the yield not being comparable to other oxidative Heck products, being able to introduce the bromo functionality is advantageous as it provides a handle for further reactions such as Pd(0) cross-couplings.

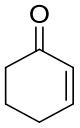
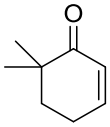
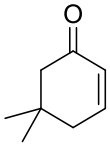
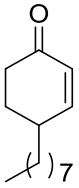
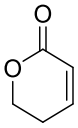
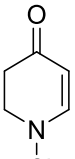
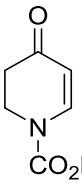
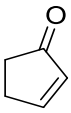
To complete our investigations an additional reaction was carried out whereby commercial boronic acid (taken straight from the bottle) was used in the reaction along with 1.5 equivalents of water in order to force the equilibrium towards the aryl boronic acid *in situ*. This reaction gave the oxidative Heck product **38e** in good yield (66%, Entry 11) which is comparable to the yield obtained when recrystallised boronic acid is used (Table 15, Entry 3). However, when the arylboronic acid was used, some conjugate addition product was also formed rather than exclusively oxidative Heck product **38e**. Despite this, the yield of oxidative Heck product when the aryl boronic acid is used is still considerably higher than when the aryl boroxine is used, even though with the latter coupling partner solely oxidative Heck product was formed.

2.5.3 Oxidative Heck reaction – substrate screen

The next part of this project was to investigate the substrate scope of the oxidative Heck reaction. This substrate screen was carried out by other members of the Lee group, but it is included for completeness.

The catalyst was chosen according to the type of substrate; the *in situ* generated catalyst (conditions A, Table 16) was found to be best for more sterically hindered substrates and the premade catalyst $Pd(MeCN)_4(OTf)_2$ (conditions B, Table 16) was suited to more electron-rich substrates. Optimisation of the reaction conditions also found that 5 mol% catalyst was sufficient for the majority of substrates. Results from the substrate screen using tris(*p*-methoxyphenyl)boroxine **6c** are shown below (Table 16). The same substrates were used for this screen as were used in the conjugate addition work so that direct comparisons could be drawn between oxidative Heck and conjugate addition results and demonstrate the switching between reaction products which occurs when a different solvent is used. Comparison between results for oxidative Heck and conjugate addition reactions for each substrate will be discussed in more detail in section 2.5.4.



Entry	Substrate	Catalyst	Isolated yield (%)
1	 **37**	A	**38c** 84%
2	 **129**	A	**138c** 57%
3[a,b]	 **130**	A	**139c** 60%
4[b]	 **126**	A	**140c** 38% conv.
5[b]	 **101**	A	**103c** 66%
6[b,c]	 **131**	B	**141c** 50%
7[b,c]	 **132**	B	**142c** 80%
8[d]	 **82**	A	**114c** 32%

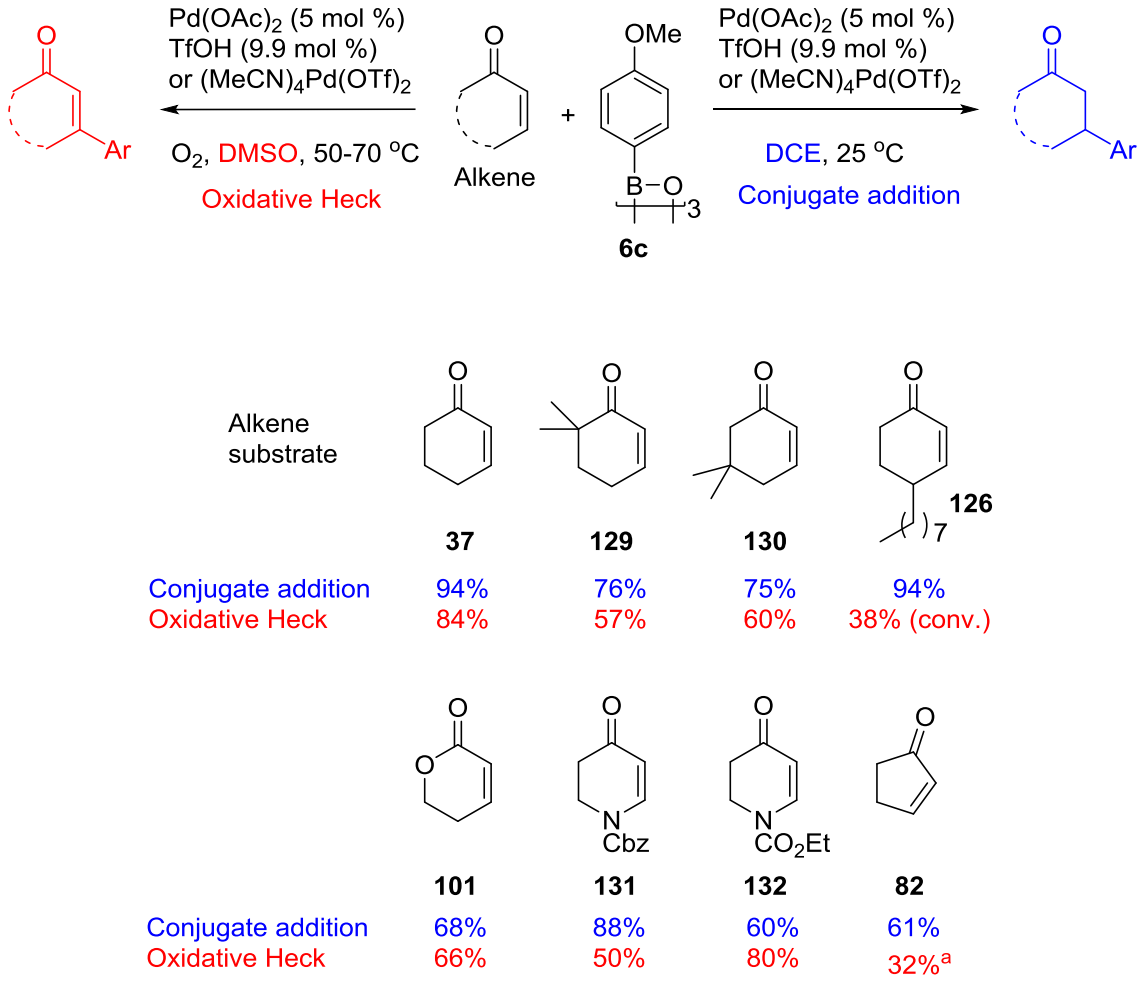
[a]70 °C, 3:1 substrate:boroxine. [b]$NaNO_3$ added (1-2 equiv). [c]10 + 5 mol% catalyst, 2 + 0.5 equiv. boroxine. [d]5 + 5 mol% catalyst, 2 + 2 equiv. boroxine, 1:1 conjugate addition:oxidative Heck.

Table 16: Oxidative Heck reaction substrate screen

With the exception of cyclopenten-2-one **82** which gave a 1:1 ratio of oxidative Heck to conjugate addition product (Entry 8), all of the substrates formed the oxidative Heck product in good to excellent yield. Yields were decent to very good for sterically hindered substrates (**129** and **130,** Entries 2 and 3). A slightly higher temperature was found to be necessary to give product **139c**, in addition to using reverse stoichiometry of the substrate to boroxine (3:1). γ-Substituted cyclohexenones **126** give quite poor conversion, presumably due to the proximity of the substituent to the reactive alkene centre (Entry 4). More electron-rich substrates (**101, 131** and **132,** Entries 5-7) also give reasonable to very good yields of the oxidative Heck product.

2.5.4 Substrate screen – comparison between oxidative Heck and conjugate addition results

In order to compare yields of oxidative Heck to conjugate addition products for each substrate, the yields for both reactions are compiled and shown below (Figure 1).



[a]1:1 oxidative Heck:conjugate addition product formed. Isolated yield of oxidative Heck product = 32%

Figure 1: Controlled switching between oxidative Heck and conjugate addition reactions – substrate screen

Using various cyclic enone substrates and tris(*p*-methoxyphenyl)boroxine, we have successfully been able to switch the reaction outcome from conjugate addition product to oxidative Heck product by changing the solvent from dichloroethane to DMSO.

A wide range of substrates with various steric and electronic properties are tolerant of both sets of reaction conditions. Generally yields are good to excellent for conjugate

addition reactions. A slight decrease in yield is seen for oxidative Heck reactions (with the exception of **132**) but this is unsurprising given that cyclic enones are challenging substrates for oxidative Heck reactions. Our studies found that whilst substituents close to the reactive alkene centre do not hinder the conjugate addition reaction, they do retard the oxidative Heck somewhat (Figure 1). Additionally, we have found that the premade catalyst $(MeCN)_4Pd(OTf)_2$ is suited to more electron-rich substrates for both conjugate addition and oxidative Heck reactions whilst the *in situ* generated catalyst $[Pd(OTf)_2]$ performs well for more sterically hindered substrates.

2.5.5 Boronic acid screen – comparison between oxidative Heck and conjugate addition results

Having conducted a boronic acid screen for both conjugate addition and oxidative Heck reactions, the results for both reactions are shown in the figure below for comparison (Figure 2).

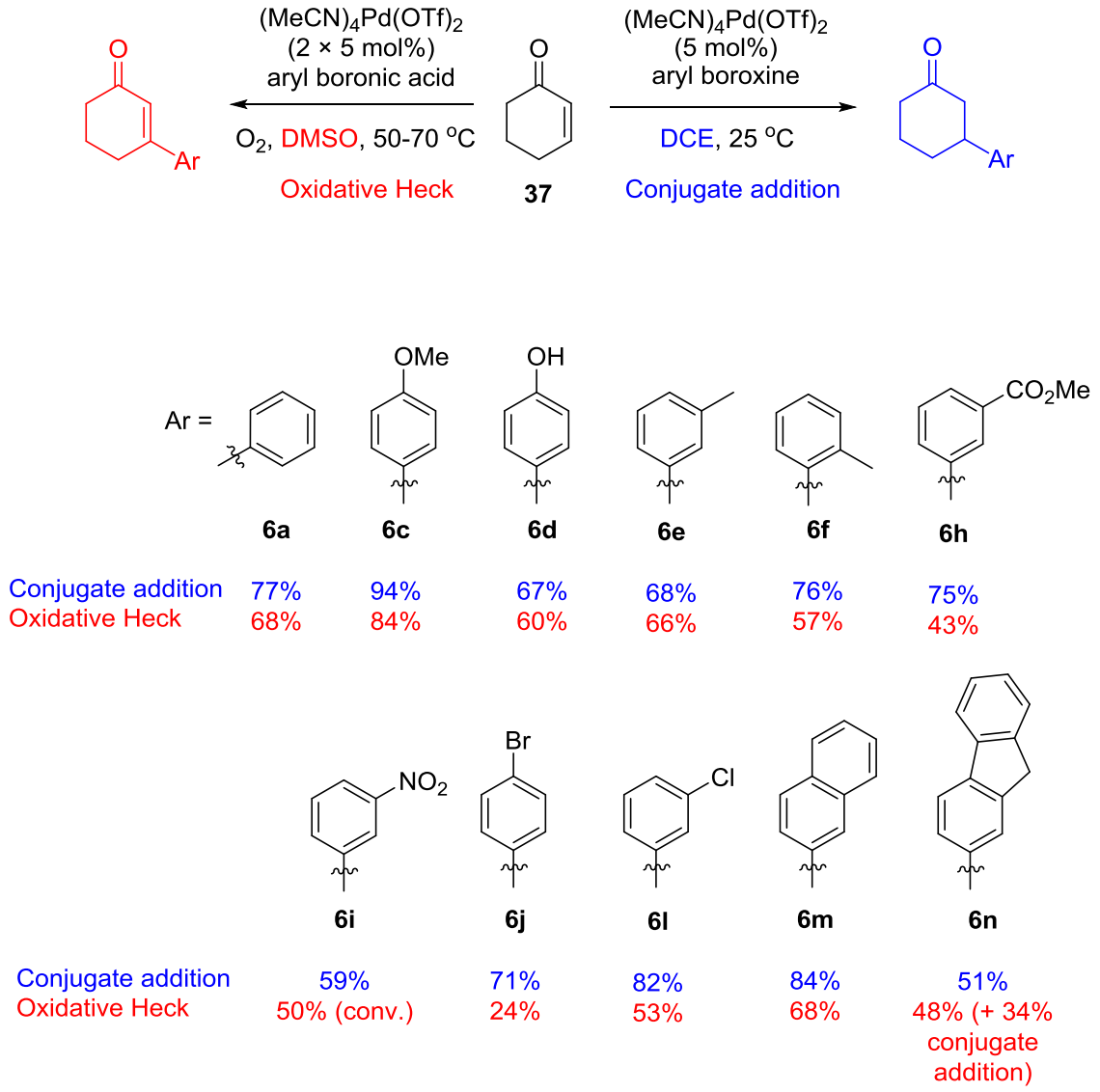


Figure 2: Controlled switching between oxidative Heck and conjugate addition reactions – boronic acid/boroxine screen

As previously discussed in section 2.4.2 (Table 3), conjugate addition reactions of 2-cyclohexen-1-one **37** with a range of boroxines gave good to excellent yields using the premade catalyst $(MeCN)_4Pd(OTf)_2$. Using the same catalyst and aryl boronic acids

rather than the corresponding boroxine, oxidative Heck reactions proceeded in moderate to excellent yields. The majority of boronic acids with the exception of 2-fluorene boronic acid **6n** demonstrated efficient switching from conjugate addition to oxidative Heck product on changing the reaction solvent. Yields showed a similar trend to the substrate screen in that they were lower for the oxidative Heck reactions, which again reflects the fact that this reaction is more challenging than conjugate addition. Despite this, a clear switching from exclusively conjugate addition product to oxidative Heck product can be observed from these results.

2.5.6 Catalyst studies – carried out by J. Boehnke

In order to shed light on factors which affect the switching between oxidative Heck and conjugate addition reactions, we decided to investigate the identity of the catalyst in DMSO. By adding four equivalents of DMSO to a solution of the catalyst $(MeCN)_4Pd(OTf)_2$ in chloroform and growing a crystal from the solution, the complex $(DMSO)_4Pd(OTf)_2$ was identified by X-ray analysis. The complex has 2 *S*-bound and 2 *O*-bound DMSO molecules in a *cis* geometry (Figure 3).

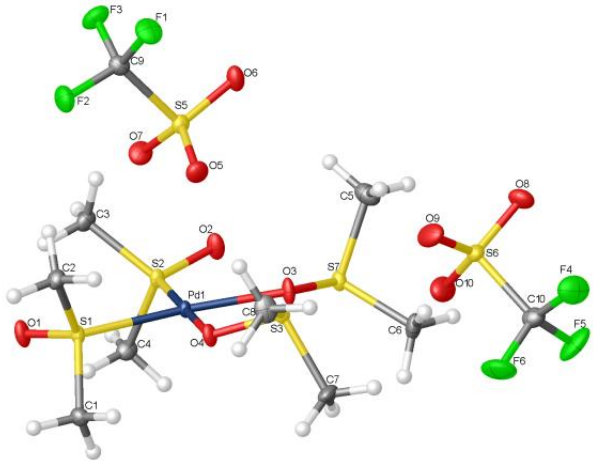
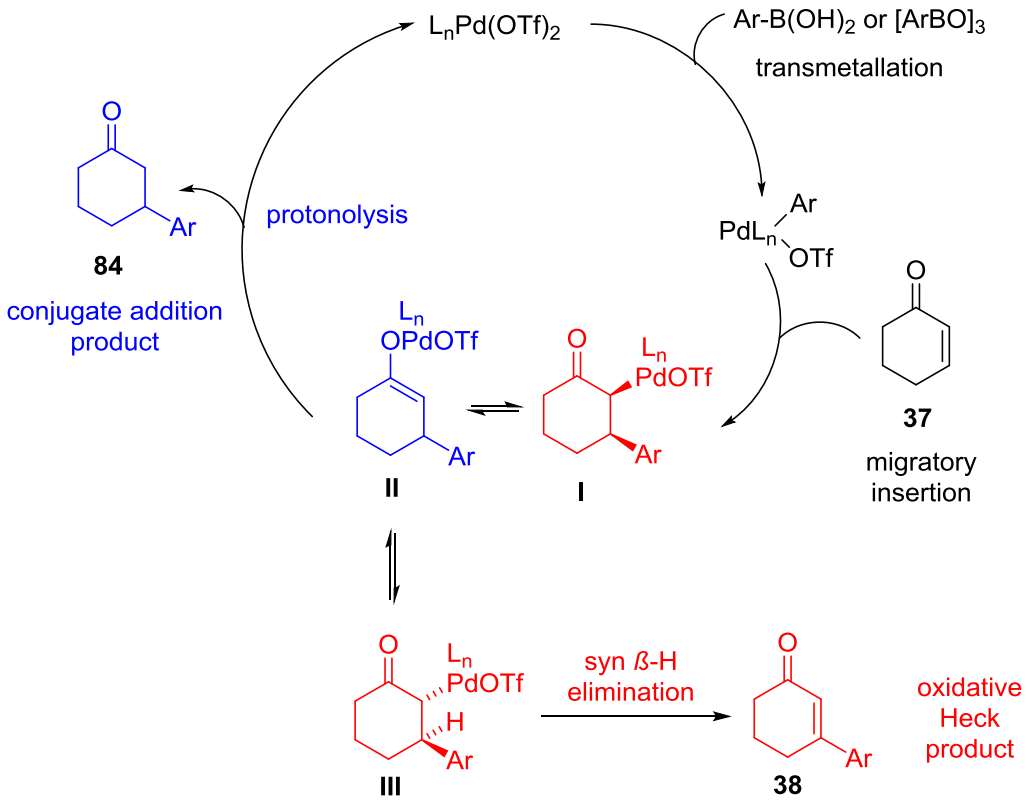


Figure 3: Crystal structure of $(DMSO)_4Pd(OTf)_2$

Formation of the complex shown in Figure 3 confirmed our hypothesis that the more polar and coordinating DMSO (as opposed to non-polar dichloroethane) possibly ligates to palladium during the oxidative Heck reaction. This ligation perhaps stabilises the cationic palladium centre in a way that promotes the oxidative Heck reaction pathway rather than formation of the conjugate addition product. These two pathways are discussed below (section 2.5.7).

2.5.7 Mechanism



Scheme 61: Proposed catalytic cycle for oxidative Heck and conjugate addition reactions

The mechanisms for both oxidative Heck and conjugate addition reactions begin with the same two steps; transmetallation of the arylboron species onto palladium, followed by migratory insertion of the alkene substrate (e.g. **37)** to give intermediate **I** (Scheme 61). It is at this point in the catalytic cycle that the two mechanisms diverge to form either the oxidative Heck (**38**) or conjugate addition product (**84**).

Intermediate **I** can undergo protonolysis either directly or more likely *via* enolate **II** to form the conjugate addition product **84**. Alternatively, in order for the oxidative Heck product to be formed, *syn* β-hydride elimination needs to be facilitated. Intermediate **I** is sterically precluded from undergoing *syn* β-hydride elimination and thus epimerisation of **I** to **III** *via* **II** takes place before this final step to form the oxidative Heck product **38**.[*]

[*]Alternatively, a boron enolate species could be formed during the mechanistic cycle as opposed to the palladium enolate shown in Scheme 61.

From our studies, we have found that more polar solvents favour oxidative Heck reactions and therefore must promote the *syn* β-hydride elimination step over protonolysis, whereas the conjugate addition pathway is more favoured when dichloroethane is used as a solvent. Following on from X-ray analysis of the catalyst $Pd(MeCN)_4(OTf)_2$ in DMSO as discussed above (section 2.5.6), the ligation of DMSO to palladium may be stabilising the metal centre in such a way that *syn* β-hydride elimination is promoted, by affecting the equilibrium between **I**, **II** and **III**.

It is possible that DMSO ligation forms a softer Pd centre which prefers the softer C-bound enolate **III** over the O-bound enolate **II,** thus promoting the epimerisation to **III** to allow *syn* β-hydride elimination.

A second possible reaction pathway to give the oxidative Heck product **38** would be *via* conjugate addition followed by oxidation.[27] However, after subjecting conjugate addition product **84** to the oxidative Heck reaction conditions, only trace oxidative Heck product was formed thus confirming that the oxidative Heck products are indeed formed *via* the proposed pathway.

2.6 Conclusions

We have successfully developed methodology to efficiently switch the outcome of the ligand- and base-free Pd(II)-catalysed reaction between cyclic enones and boronic acids from conjugate addition to oxidative Heck product by changing the solvent. The reaction is tolerant of a variety of aryl boronic acids and substrates and proceeds in good yields. We found that whilst aryl boroxines are required for the conjugate addition reaction, aryl boronic acids are preferred for the oxidative Heck reaction. We have also investigated reasons for this switch and our studies have found that more polar solvents promote oxidative Heck over conjugate addition. Dichloroethane was the most suitable solvent for conjugate addition reactions whereas the oxidative Heck product was formed preferentially when DMSO was used. Possible reasons for this include ligation of DMSO to palladium which perhaps stabilises the metal centre and facilitates the *syn* β-hydride elimination step leading to formation of the oxidative Heck over conjugate addition product.

2.7 Experimental Section

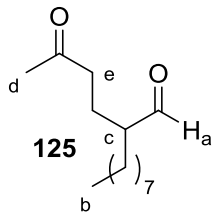
^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26 ppm, δ_C at 77.00 ppm, $(CD_3)_2CO$ at δ_H 2.05 ppm, δ_C at 29.84 ppm or C_6D_6 at δ_H 7.16 ppm, δ_C at 128.06 ppm). *J* values are given in Hz and s, d, dd, t, q, qn and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Br, v str, str, w represent broad, very strong, strong and weak respectively. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate.

Petrol ether refers to petroleum ether (40–60 ^{o}C). Dichloroethane (DCE) was purchased from Alfa Aesar and used without further purification. d_6-Dimethylsulfoxide (d_6-DMSO) was purchased from Cambridge Isotope Laboratories. 2-Cyclohexen-1-one was purchased from Fluka and Sigma Aldrich. All oxidative Heck reactions were run under an O_2 atmosphere provided by a balloon filled with O_2 supplied by BOC. All arylboronic acids were purchased from Sigma-Aldrich, Fluorochem or Acros. Commercially available boronic acids contain varying amounts of their corresponding anhydride.

Preparation of boroxine: Where the boroxine was used for reactions, it was prepared by heating the relevant boronic acid under vacuum until the crystalline solid became flocculent, silica like particles. RMM of the boroxine used in calculations is actually 1/3 RMM to represent one Ar-B-O unit given the boroxine exists in trimeric form.

Substrate synthesis

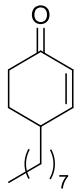
2-(3-Oxobutyl)decanal (125)[26, 28]



Decanal (8.35 mL, 6.93 g, 0.0443 mol) was added to a dried, sealed vessel. Diethylamine (0.92 mL, 0.65 g, 8.89 mmol) was added followed by dry THF (475 mL) *via* canula. The resulting solution was stirred and 3-buten-2-one (5.34 mL, 4.61 g, 0.066 mmol) was added followed by THF (10 mL). The reaction mixture was left to stir at 80 °C for 70 hours after which it was left to cool, concentrated under reduced pressure and purified by flash column chromatography using a gradient eluent system 20:1→7:1 hexane:ethyl acetate to afford a yellow oil **125** (6.00 g, 0.0265 mol, 60%).

R_f 0.42 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.54 (d, J = 2.8 Hz, 1H, H_a), 2.56 – 2.33 (m, 2H, H_e), 2.30 – 2.18 (m, 1H, H_c), 2.12 (s, 3H, H_d), 1.94 – 1.56 (m, 4H, alkyl CH_2), 1.51 – 1.36 (m, 2H, alkyl CH_2), 1.36 – 1.15 (m, 10H, alkyl CH_2), 0.86 (t, J = 6.7 Hz, 3H, H_b); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.8 (C), 204.8 (C), 51.1 (CH), 40.6 (CH_2), 31.7 (CH_2), 29.9 (CH_3), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 26.9 (CH_2), 22.5 (CH_2), 22.2 (CH_2), 14.0 (CH_3); ν_{max}/cm^{-1} 2924 str, 2855 str, 1719 str, 1458 w.

4-Octyl-2-cyclohexen-1-one (126)[26, 28]

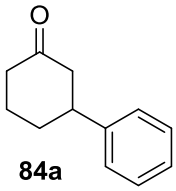

126

2-(3-Oxobutyl)decanal **125** (6.00 g, 0.0265 mol) was dissolved in THF (59 mL) and Et_2O (226 mL). Potassium hydroxide (5%) solution (208 ml) was added followed by $^{n}Bu_4NOH$ 40% solution in H_2O (14 mL, 13.9 g, 0.0214 mol). The resulting solution was heated to reflux under N_2 for 5 hours before it was removed from heat and stored in a freezer overnight then returned to reflux for a further 1 hour. On completion, the reaction was left to cool, washed with brine (20 mL) and the aqueous phase was washed with Et_2O (3 × 20 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography using a gradient eluent system 18:1→15:1 petroleum ether:EtOAc to afford a yellow oil **126** (2.43 g, 0.0117 mol, 44%).

R_f 0.53 (7:1 petroleum ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 – 6.81 (m, 1H), 6.03 – 5.92 (m, 1H), 2.64 – 2.26 (m, 3H), 2.24 – 1.97 (m, 1H), 1.79 – 1.59 (m, 1H), 1.58 – 1.14 (m, 14H), 0.98 – 0.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0 (C), 155.4 (CH), 128.8 (CH), 36.9 (CH_2), 36.0 (CH), 34.5 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3); ν_{max}/cm^{-1} 2924 str, 2854 str, 1679 str, 1457 w.

Synthesis of conjugate addition products

3-Phenylcyclohexanone (84a)[29]

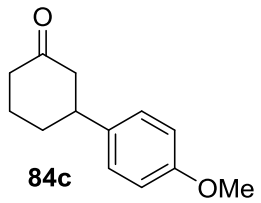


84a

$Pd(MeCN)_4(OTf)_2$ (7.0 mg, 12.3 μmol) and $NaNO_3$ (42.8 mg, 0.504 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture stirred for 5 minutes. 2-Cyclohexen-1-one **37** (24.6 mg, 0.251 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 ml) to afford a dark orange solution. Phenyl boroxine (78.6 mg, 0.756 mmol) was added and the mixture was sonicated for 2 minutes. The reaction mixture was left to stir at 25 °C for 40 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using an eluent system 10:1 hexane:EtOAc to afford **84a** as a yellow oil (33.5 mg, 0.193 mmol, 77%).

R_f 0.32 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 – 7.33 (m, 2H, Ar-H), 7.28 – 7.23 (m, 3H, Ar-H), 3.09 – 2.98 (m, 1H, C<u>H</u>Ar), 2.65 – 2.35 (m, 4H, CH_2), 2.22 – 2.09 (m, 2H, CH_2), 1.94 – 1.73 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.0 (C), 144.3 (C), 128.6 (CH), 126.6 (CH), 126.5 (CH), 48.9 (CH_2), 44.7 (CH), 41.2 (CH_2), 32.7 (CH_2), 25.5 (CH_2); ν_{max}/cm^{-1} 2938 str, 2865 str, 1711 v str, 1497 m, 1451 m, 756 w, 700 str.

3-(4-Methoxyphenyl)cyclohexanone (84c)[30]



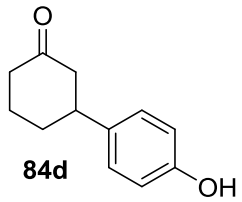
84c

$Pd(MeCN)_4(OTf)_2$ (7.4 mg, 12.9 μmol) and $NaNO_3$ (43.0 mg, 0.506 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture stirred for 5 minutes. 2-Cyclohexen-1-one **37** (24.3 mg, 0.253 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 ml) to afford an orange solution. Tris(4-methoxyphenyl)boroxine (100.6 mg, 0.751 mmol) was added and the mixture was sonicated for 2 minutes. The reaction mixture was left to stir at 25 °C for 24 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using an eluent system 10:1 hexane:EtOAc to afford **84c** as a yellow oil (38.5 mg, 0.188 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, J = 8.8 Hz, 2H, Ar-H), 6.86 (d, J = 8.8 Hz, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 3.02–2.90 (m, 1H, C<u>H</u>Ar), 2.56 (ddt, J = 14.0, 4.6, 1.9 Hz, 1H, COC<u>H</u>HCHAr), 2.52–2.47 (m, 1H, COCH<u>H</u>CHAr), 2.47–2.30 (m, 2H, CH_2), 2.20–1.97 (m, 2H, CH_2), 1.86–1.67 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.1 (C), 158.3 (C), 136.6 (C), 127.5 (CH), 114.0 (CH), 55.2 (CH_3), 49.2 (CH_2), 43.9 (CH), 41.1 (CH_2), 33.0 (CH_2), 25.5 (CH_2); ν_{max}/cm^{-1} 2935, 1707, 1611, 1512, 1245.

Note: A higher yield of product **84c** (94%) was obtained by Steven Levey using conditions optimised for the conjugate addition substrate screen (IR data and NMR spectra obtained by S. Levey). This result is detailed in section 2.4.4 and additionally in the publication of this work.[22] However, the lower yield obtained by the author and the method used is given in this section for completeness.

3-(4-Hydroxyphenyl)cyclohexanone (84d)[31]

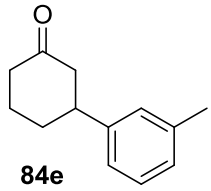


84d

$Pd(MeCN)_4(OTf)_2$ (6.8 mg, 12.0 μmol) and $NaNO_3$ (42.7 mg, 0.502 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture stirred for 5 minutes. 2-Cyclohexen-1-one **37** (23.7 mg, 0.247 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 mL) to afford an orange solution. 4-Hydroxyphenyl boroxine (89.5 mg, 0.746 mmol) was added and the solution was sonicated for 2 minutes, during which the solution turned bright pink. The reaction mixture was left to stir at 25 °C for 24 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using a gradient eluent system 10:1→3:1 hexane:EtOAc to afford **84d** as a yellow amorphous solid (31.3 mg, 0.165 mmol, 67%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (d, J = 8.5 Hz, 2H, Ar-H), 6.81 (d, J = 8.5 Hz, 2H, Ar-H), 5.72 (s, 1H, OH), 3.01 – 2.89 (m, 1H, C<u>H</u>Ar), 2.64 – 2.30 (m, 4H, CH_2), 2.23 – 1.95 (m, 2H, CH_2), 1.90 – 1.65 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.3 (C), 154.5 (C), 136.3 (C), 127.6 (CH), 115.5 (CH), 49.1 (CH_2), 43.9 (CH), 41.2 (CH_2), 32.9 (CH_2), 25.4 (CH_2); ν_{max}/cm^{-1} 3322 br str, 2940 w, 1693 v str, 1516 v str, 1446 str, 1222 v str.

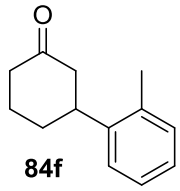
3-*m*-Tolyl-cyclohexanone (84e)[32]


84e

$Pd(MeCN)_4(OTf)_2$ (7.1 mg, 12.5 μmol) and $NaNO_3$ (42.0 mg, 0.494 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture was stirred for 5 minutes. 2-Cyclohexen-1-one **37** (24.0 mg, 0.250 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 ml) to afford a dark orange solution. *m*-Tolyl boroxine (88.5 mg, 0.750 mmol) was added and the mixture was sonicated for 2 minutes. The reaction mixture was left to stir at 25 °C for 42 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using an eluent system 12:1 hexane:EtOAc to afford **84e** as a yellow oil (32.2 mg, 0.171 mmol, 68%).

R_f 0.36 (5:1 hexane:EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.29 – 7.23 (m, 1H, Ar-H), 7.10 – 7.04 (m, 3H, Ar-H), 3.06 – 2.95 (m, 1H, C<u>H</u>Ar), 2.66 – 2.38 (m, 4H, CH_2), 2.38 (s, 3H, CH_3), 2.22 – 2.08 (m, 2H, CH_2), 1.95 – 1.72 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.1 (C), 144.3 (C), 138.2 (C), 128.5 (CH), 127.4 (CH), 127.3 (CH), 123.5 (CH), 49.0 (CH_2), 44.7 (CH), 41.2 (CH_2), 32.8 (CH_2), 25.6 (CH_2), 21.4 (CH_3); ν_{max}/cm^{-1} 2936 str, 2865 str, 1711 v str, 1222 str, 782 str, 702 str.

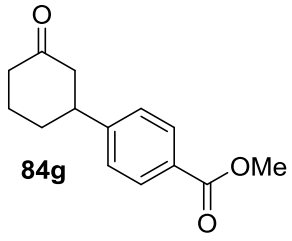
3-*o*-Tolylcyclohexanone (84f)[32]


84f

$Pd(MeCN)_4(OTf)_2$ (7.1 mg, 12.5 μmol) and $NaNO_3$ (42.5 mg, 0.500 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture was stirred for 5 minutes. 2-Cyclohexen-1-one **37** (24.3 mg, 0.253 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 mL). The solution was stirred for 25 minutes to afford a green solution. *o*-Tolyl boroxine (88.3 mg, 0.748 mmol) was added and the mixture was sonicated for 2 minutes. The reaction mixture was left to stir at 25 °C for 42 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using a gradient eluent system 12:1→10:1 hexane:EtOAc to afford **84f** as a yellow oil (35.7 mg, 0.190 mmol, 76%).

R_f 0.38 (5:1 hexane:EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 – 7.22 (m, 2H, Ar-H), 7.19 – 7.11 (m, 2H, Ar-H), 3.27 – 3.17 (m, 1H, C<u>H</u>Ar), 2.54 – 2.37 (m, 4H, CH_2), 2.33 (s, 3H, CH_3), 2.22 – 2.12 (m, 1H, CH_2), 2.05 – 1.99 (m, 1H, CH_2), 1.92 – 1.72 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.2 (C), 142.2 (C), 135.0 (C), 130.6 (CH), 126.4 (CH), 126.3 (CH), 125.0 (CH), 48.3 (CH_2), 41.2 (CH_2), 40.2 (CH), 31.9 (CH_2), 25.7 (CH_2), 19.2 (CH_3); ν_{max}/cm^{-1} 3021 str, 2937 str, 2865 str, 1709 v str, 1223 str, 752 str.

3-(4-(Methoxycarbonyl)phenyl)cyclohexanone (84g)[33]

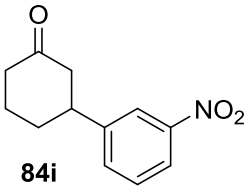


84g

$Pd(MeCN)_4(OTf)_2$ (7.1 mg, 0.012 mmol) and $NaNO_3$ (42.9 mg, 0.505 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture was stirred for 5 minutes. 2-Cyclohexen-1-one **37** (24.2 mg, 0.252 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 mL). 4-Methoxycarbonylphenyl boroxine (90.4 mg, 0.558 mmol) was added and the solution was left to stir at 25 °C for 20 hours. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using an eluent system 10:1 hexane:EtOAc to afford a yellow oil **84g** (42.0 mg, 0.181 mmol, 72%).

R_f 0.26 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.3 Hz, 2H, Ar-H), 7.28 (d, J = 8.3 Hz, 2H, Ar-H), 3.89 (s, 3H, OCH_3), 3.14 – 2.98 (m, 1H, C<u>H</u>-Ar), 2.65 – 2.29 (m, 4H, CH_2), 2.22 – 2.01 (m, 2H, CH_2), 1.96 – 1.67 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.3 (C), 166.8 (C), 149.4 (C), 130.0 (CH), 128.6 (C), 126.6 (CH), 52.0 (CH_3), 48.4 (CH_2), 44.6 (CH), 41.1 (CH_2), 32.4 (CH_2), 25.4 (CH_2); ν_{max}/cm^{-1} 2952 str, 2861 str, 1717 v str, 1281 v str, 1109 str, 769 str, 706 str.

3-(2-Nitrophenyl)cyclohexanone (84i)[29]

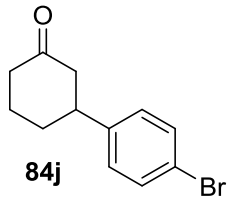


84i

$Pd(MeCN)_4(OTf)_2$ (7.3 mg, 12.8 μmol) and $NaNO_3$ (42.8 mg, 0.504 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture stirred for 5 minutes. 2-Cyclohexen-1-one **37** (24.0 mg, 0.250 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 mL) to afford an orange solution. 3-Nitrophenyl boroxine (112 mg, 0.752 mmol) was added and the mixture was sonicated for 2 minutes. The reaction mixture was left to stir at 25 °C for 66 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using an eluent system 5:1 hexane:EtOAc to afford **84i** as a yellow amorphous solid (32.2 mg, 0.147 mmol, 59%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 – 8.07 (m, 2H, Ar-H), 7.56 – 7.47 (m, 2H, Ar-H), 3.18 – 3.07 (m, 1H, C<u>H</u>Ar), 2.65 – 2.34 (m, 4H, CH_2), 2.22 – 2.10 (m, 2H, CH_2), 1.97 – 1.74 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.8 (C), 148.4 (C), 146.3 (C), 133.0 (CH), 129.6 (CH), 121.8 (CH), 121.4 (CH), 48.4 (CH_2), 44.2 (CH), 40.9 (CH_2), 32.4 (CH_2), 25.3 (CH_2); ν_{max}/cm^{-1} 2940 w, 2867 w, 1708 v str, 1522 v str, 1347 str.

3-(4-Bromophenyl)cyclohexanone (84j)[34]

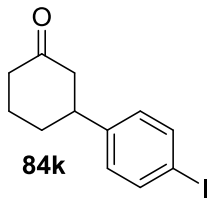


84j

$Pd(MeCN)_4(OTf)_2$ (7.6 mg, 13.3 μmol) and $NaNO_3$ (42.1 mg, 0.495 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture was stirred for 5 minutes. 2-Cyclohexen-1-one **37** (24.6 mg, 0.256 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 mL) to afford an orange solution. 4-Bromophenyl boroxine (137 mg, 0.751 mmol) was added and the mixture was sonicated for 2 minutes. The reaction mixture was left to stir at 25 °C for 23 hours under an atmosphere of oxygen. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using a gradient eluent system 10:1→8:1 hexane:EtOAc to afford **84j** as a yellow oil (46.1 mg, 0.182 mmol, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.4 Hz, 2H, Ar-H), 7.09 (d, J = 8.4 Hz, 2H, Ar-H), 3.02 – 2.92 (m, 1H, C<u>H</u>-Ar), 2.60 – 2.31 (m, 4H, CH_2), 2.18 – 1.99 (m, 2H, CH_2), 1.88 – 1.68 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5 (C), 143.2 (C), 131.7 (CH), 128.3 (CH), 120.3 (C), 48.7 (CH_2), 44.1 (CH), 41.1 (CH_2), 32.6 (CH_2), 25.4 (CH_2); ν_{max}/cm^{-1} 2940 w, 2865 w, 1715 v str, 1490 str, 821 str.

3-(4-Iodophenyl)cyclohexanone (84k)

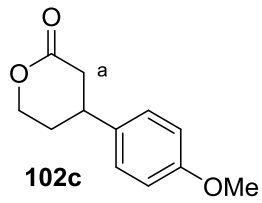


84k

$Pd(MeCN)_4(OTf)_2$ (7.1 mg, 0.012 mmol) and $NaNO_3$ (41.6 mg, 0.489 mmol) were added to a flask followed by DCE (1 mL) and the resulting mixture was stirred for 5 minutes. 2-Cyclohexen-1-one **37** (23.7 mg, 0.247 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 mL) to afford an orange solution. 4-Iodophenyl boroxine **15** (174 mg, 0.754 mmol) was added and the resulting light brown solution was sonicated for 2 minutes. The solution was left to stir at 25 °C for 20 hours. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using an eluent system 10:1 hexane:EtOAc to afford a yellow amorphous solid **84k** (30.8 mg, 0.103 mmol, 42%).

R_f 0.33 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.3 Hz, 2H, Ar-H), 6.97 (d, J = 8.3 Hz, 2H, Ar-H), 3.01 – 2.90 (m, 1H, C<u>H</u>-Ar), 2.60 – 2.31 (m, 4H, CH_2), 2.19 – 2.03 (m, 2H, CH_2), 1.88 – 1.72 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.4 (C), 143.9 (C), 137.7 (CH), 128.6 (CH), 91.8 (C), 48.63 (CH_2), 44.2 (CH), 41.1 (CH_2), 32.6 (CH_2), 25.4 (CH_2); ν_{max}/cm^{-1} 2935 w, 2863 w, 1709 v str, 1486 str, 817 str; HRMS (APCI) calculated for $[M+H]^+$ 301.0084, $C_{12}H_{14}OI$ found: 301.0088.

4-(4'-Methoxyphenyl)tetrahydro-2H-pyran-2-one (102c)[18]



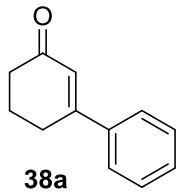
102c

$Pd(MeCN)_4(OTf)_2$ (7.6 mg, 13.3 μmol) was added to a flask followed by DCE (1 mL) and the resulting solution stirred for 5 minutes. 5,6-Dihydro-2*H*-pyran-2-one **101** (90%, 27.7 mg, 0.254 mmol) was weighed and added *via* pasteur pipette, washing the pipette with additional DCE (4 ml). 4-Methoxyphenylboroxine (100.0 mg, 0.746 mmol) was added followed by $NaNO_3$ (43.3 mg, 0.509 mmol) and the solution was sonicated for 30 seconds. The solution was left to stir at 30 °C for 48 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using an eluent system 12:1→3:1 hexane:EtOAc to afford a colourless amorphous solid **102c** (35.6 mg, 0.173 mmol, 68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 – 7.06 (m, 2H, Ar-H), 7.01 – 6.82 (m, 2H, Ar-H), 4.57 – 4.29 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.27 – 3.10 (m, 1H, C<u>H</u>Ar), 2.89 (ddd, *J* = 17.6, 5.9, 1.7 Hz, 1H, H_a), 2.58 (dd, *J* = 17.6, 10.6 Hz, 1H, $H_{a'}$), 2.22 – 1.89 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8 (C), 158.6 (C), 134.8 (C), 127.4 (CH), 114.2 (CH), 68.6 (CH_2), 55.3 (CH_3), 37.7 (CH_2), 36.6 (CH), 30.4 (CH_2); ν_{max}/cm^{-1} 2960, 1727, 1513, 1246, 1220, 1071, 1030, 830.

Synthesis of oxidative Heck products

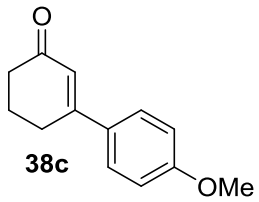
3-Phenyl-2-cyclohexen-1-one (38a)[29]


38a

$Pd(MeCN)_4(OTf)_2$ (4.1 mg, 7.2 μmol) and d_6-DMSO (0.10 mL) were added to a flask and the reaction was stirred for 10 minutes. 2-Cyclohexen-1-one **37** (12.3 mg, 0.128 mmol) was added *via* pasteur pipette, washing the pipette with additional d_6-DMSO (0.40 mL). Phenylboroxine (26.7 mg, 0.257 mmol) was added and the solution changed colour from orange to yellow. A condenser was fitted and the reaction left to stir at 50 °C under a balloon of O_2. After 19.5 h, additional portions of $Pd(MeCN)_4(OTf)_2$ (3.7 mg, 6.47 μmol) and phenylboroxine (26.4 mg, 0.254 mmol) were added and the reaction left to stir at 50 °C under an O_2 atmosphere for another 22 h. On completion, EtOAc (20 mL) was added and the reaction mixture was washed with brine (20 mL) and the aqueous phase washed with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography using a gradient eluent system 12:1 hexane:EtOAc to afford **38a** as a yellow oil (15.0 mg, 0.0871 mmol, 68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 – 7.49 (m, 2H, Ar-H), 7.47 – 7.38 (m, 3H, Ar-H), 6.42 (t, J = 1.5 Hz, 1H, C=C<u>H</u>), 2.78 (td, J = 6.2, 1.5 Hz, 2H, CH_2), 2.49 (t, J = 6.2 Hz, 2H, CH_2), 2.16 (qn, J = 6.2 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0 (C), 159.8 (C), 138.8 (C), 130.0 (CH), 128.7 (CH), 126.1 (CH), 125.4 (CH), 37.3 (CH_2), 28.1 (CH_2), 22.8 (CH_2); ν_{max}/cm^{-1} 2939 w, 1663 str, 1603 str, 1445 w, 758 str, 693 str.

3-(4-Methoxyphenyl)-2-cyclohexen-1-one (38c)[29]



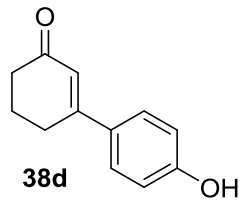
38c

$Pd(MeCN)_4(OTf)_2$ (4.2 mg, 7.3 μmol) and d_6-DMSO (0.20 mL) were added to a flask. 2-Cyclohexen-1-one **37** (12.6 mg, 0.131 mmol) was added *via* pasteur pipette, washing the pipette with additional d_6-DMSO (0.30 mL). Tris(*p*-methoxyphenyl)boroxine (33.7 mg, 0.252 mmol) was added and the solution changed colour from orange to yellow. A condenser was fitted and the reaction left to stir at 50 °C under an O_2 atmosphere. After 21 h, additional portions of $Pd(MeCN)_4(OTf)_2$ (4.3 mg, 7.5 μmol) and tris(*p*-methoxyphenyl)boroxine (33.4 mg, 0.249 mmol) were added and the reaction left to stir at 50 °C under an O_2 atmosphere for a further 22 h. On completion, EtOAc (20 mL) was added and the reaction mixture was washed with brine (20 mL) and the aqueous phase washed with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography using 10:1 petrol ether:EtOAc to afford a orange amorphous solid **38c** (15.5 mg, 0.077 mmol, 58%).

R_f 0.50 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.91 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.37 (s, 1H, C=C<u>H</u>), 3.82 (s, 3H, OCH_3), 2.73 (m, 2H, CH_2), 2.45 (t, *J* = 6.2 Hz, 2H, CH_2), 2.12 (qn, *J* = 6.2 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8 (C), 161.1 (C), 159.0 (C), 130.6 (C), 127.5 (CH), 123.5 (CH), 114.0 (CH), 55.3 (CH_3), 37.1 (CH_2), 27.7 (CH_2), 22.7 (CH_2); ν_{max}/cm^{-1} 2941 str, 1644 str, 1595 str, 1570 str, 1512 str, 1232 str, 1185 str.

Note: A higher yield of product **38c** (84%) was obtained by Steven Levey using conditions optimised for the oxidative Heck substrate screen. This result is detailed in sections 2.3 and 2.5.3 and additionally in the publication of this work.[22] However, the lower yield obtained by the author and the method used is given in this section for completeness.

3-(4-Hydroxyphenyl)-2-cyclohexen-1-one (38d)

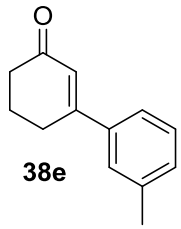


38d

$Pd(MeCN)_4(OTf)_2$ (4.4 mg, 7.7 μmol) and d_6-DMSO (0.20 mL) were added to a flask and the reaction was stirred for 10 minutes. 2-Cyclohexen-1-one **37** (12.6 mg, 0.131 mmol) was added *via* pasteur pipette, washing the pipette with additional d_6-DMSO (0.30 mL). 4-Hydroxyphenylboroxine (31.1 mg, 0.259 mmol) was added and the solution turned a brown/green colour. A condenser was fitted and the reaction left to stir at 50 °C under an O_2 atmosphere. After 19 h, additional portions of $Pd(MeCN)_4(OTf)_2$ (4.3 mg, 7.52 μmol) and 4-hydroxyphenylboroxine (31.0 mg, 0.259 mmol) were added and the reaction left to stir at 50 °C under an O_2 atmosphere for another 21 h. On completion, EtOAc (20 mL) was added and the reaction mixture was washed with brine (20 mL) and the aqueous phase washed with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography using a gradient eluent system 10:1 to 2.5:1 petroleum ether:EtOAc to afford **38d** as a red amorphous solid (14.7 mg, 0.0781 mmol, 60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, J = 8.7 Hz, 2H, Ar-H), 6.88 (d, J = 8.7 Hz, 2H, Ar-H), 6.39 (t, J = 1.5 Hz, 1H, C=C<u>H</u>), 5.45 (s, 1H, OH), 2.75 (td, J = 6.0, 1.5 Hz, 2H, CH_2), 2.54 – 2.45 (m, 2H, CH_2), 2.21 – 2.08 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2 (C), 160.7 (C), 158.4 (C), 130.2 (C), 128.0 (CH), 123.0 (CH), 115.8 (CH), 37.0 (CH_2), 27.8 (CH_2), 22.7 (CH_2); ν_{max}/cm^{-1} 3175 (br), 2944, 1703, 1633, 1571, 1512, 1441, 1352, 1266, 1245, 1177, 1136, 824 str; HRMS (APCI) calculated for $[M+H]^+$ 189.0912, $C_{12}H_{13}O_2$ found: 189.0910.

3-*m*-Tolylcyclohex-2-enone (38e)[4]



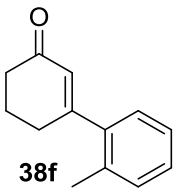
38e

$Pd(MeCN)_4(OTf)_2$ (4.2 mg, 7.3 μmol) and d_6-DMSO (0.20 mL) were added to a flask. 2-Cyclohexen-1-one **37** (12.5 mg, 0.130 mmol) was added *via* pasteur pipette, washing the pipette with additional d_6-DMSO (0.30 mL). Tris(*m*-tolyl)boroxine (30.1 mg, 0.255 mmol) was added and the solution changed colour from orange to yellow. A condenser was fitted and the reaction left to stir at 50 °C under an O_2 atmosphere. After 21 h, additional portions of $Pd(MeCN)_4(OTf)_2$ (4.1 mg, 7.2 μmol) and tris(*m*-tolyl)boroxine (30.6 mg, 0.225 mmol) were added and the reaction left to stir at 50 °C under an O_2 atmosphere for a further 19 h. On completion, EtOAc (20 mL) was added and the reaction mixture was washed with brine (20 mL) and the aqueous phase washed with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography using 10:1 petrol ether:EtOAc to afford a yellow oil **38e** (11.1 mg, 0.060 mmol, 46%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 – 7.22 (m, 4H, Ar-H), 6.43 (t, *J* = 1.4 Hz, 1H, C=C<u>H</u>), 2.80 (td, *J* = 6.1, 1.4 Hz, 2H, CH_2), 2.51 (t, *J* = 6.1 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.18 (qn, *J* = 6.1 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2 (C), 160.2 (C), 138.9 (C), 138.5 (C), 130.9 (CH), 128.8 (CH), 126.9 (CH), 125.5 (CH), 123.4 (CH), 37.4 (CH_2), 28.3 (CH_2), 23.0 (CH_2), 21.6 (CH_3); HRMS (APCI) calculated for $[M+H]^+$ 187.1117, $C_{13}H_{15}O_1$ found: 187.1116.

Note: A higher yield of product **38e** (66%) was obtained by Pauline Glen using freshly recrystallised boronic acid after further optimisation of the oxidative Heck reaction conditions. This optimisation is detailed in Table 15 and additionally in the publication of this work.[22] However, the lower yield obtained by the author and the method used is given in this section for completeness.

3-*o*-Tolylcyclohex-2-enone (38f)[4]



$Pd(MeCN)_4(OTf)_2$ (4.1 mg, 7.2 μmol) and d_6-DMSO (0.20 mL) were added to a flask. 2-Cyclohexen-1-one **37** (12.8 mg, 0.133 mmol) was added *via* pasteur pipette, washing the pipette with additional d_6-DMSO (0.30 mL). Tris(*o*-tolyl)boroxine (29.9 mg, 0.254 mmol) was added and the solution changed colour from orange to yellow. A condenser was fitted and the reaction left to stir at 50 °C under an O_2 atmosphere. After 21 h, additional portions of $Pd(MeCN)_4(OTf)_2$ (4.2 mg, 7.3 μmol) and tris(*o*-tolyl)boroxine (30.2 mg, 0.224 mmol) were added and the reaction left to stir at 50 °C under an O_2 atmosphere for a further 23 h. On completion, EtOAc (20 mL) was added and the reaction mixture was washed with brine (20 mL) and the aqueous phase washed with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography using 10:1 petrol ether:EtOAc to afford a yellow oil **38f** (11.6 mg, 0.062 mmol, 47%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 – 7.09 (m, 4H, Ar-H), 6.02 (t, J = 1.6 Hz, 1H, C=C<u>H</u>), 2.62 (td, J = 6.0, 1.6 Hz, 2H, CH_2), 2.59 - 2.48 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.24 – 2.12 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.7 (C), 163.7 (C), 140.9 (C), 134.1 (C), 130.8 (CH), 128.8 (CH), 128.5 (CH), 127.0 (CH), 126.0 (CH), 37.5 (CH_2), 31.4 (CH_2), 23.3 (CH_2), 20.2 (CH_3); HRMS (APCI) calculated for $[M+H]^+$ 187.1117, $C_{13}H_{15}O_1$ found: 187.1115.

Note: A higher yield of product **38f** (57%) was obtained by Pauline Glen using freshly recrystallised boronic acid after further optimisation of the oxidative Heck reaction conditions. This optimisation is detailed in Table 15 and additionally in the publication of this work.[22] However, the lower yield obtained by the author and the method used is given in this section for completeness.

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Chapter 3: C-H Functionalisation of Benzoquinone

All work detailed in this chapter was carried out by the author except where specified. The author would like to thank J. Jordan-Hore for his contribution to the project, particularly with optimisation work.

Chapter 3: Introduction

3.1 Background

Quinones are ubiquitous in the natural world and many compounds comprising the 1,4-benzoquinone moiety as a subunit exhibit a wide range of pharmacological applications including antibiotic, antitumour and antimalarial properties (for examples see Figure 4, **143**-**147**).[1-7] Additionally, quinones are also widely used in organic chemistry and have found uses as oxidants,[8-10] ligands,[11-15] dyes[3] and in molecular electronics.[16]

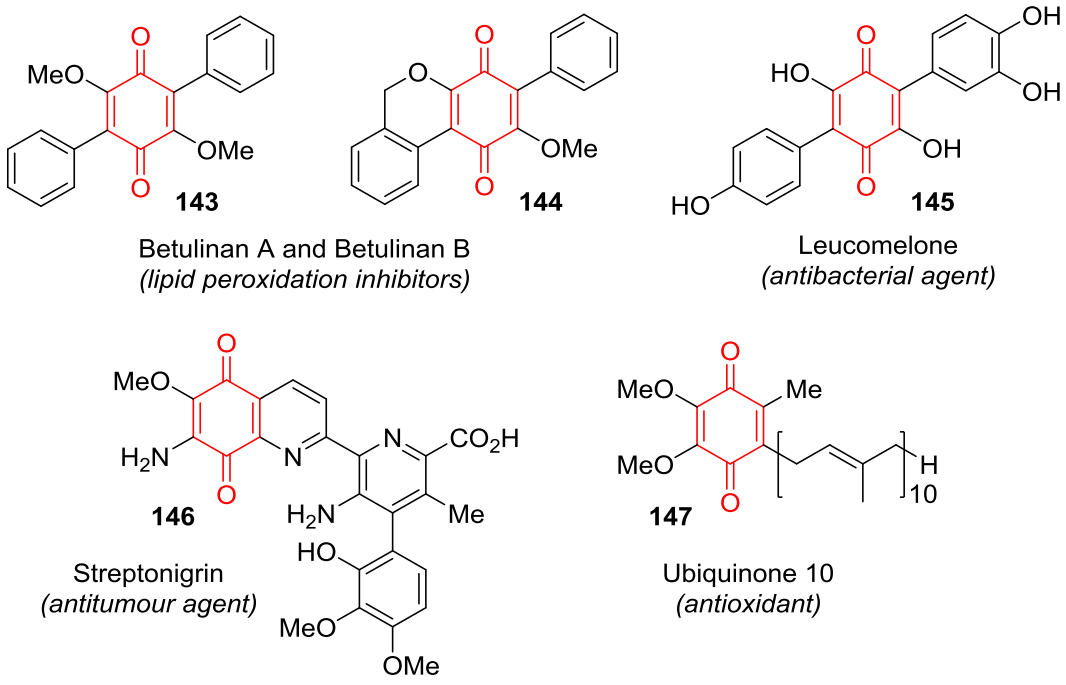


Figure 4: Examples of natural products with pharmacological properties comprising the quinone moiety

Despite the prevalence of the quinone moiety in biologically active compounds and its use in synthetic organic chemistry, the functionalisation of benzoquinone has proven challenging and often lengthy requiring multistep syntheses.[1] In synthetic chemistry, benzoquinone is more often than not used as a ligand or oxidant rather than the substrate.[1] Whilst palladium(0) cross-couplings have been employed as one method to functionalise quinones (requiring prefunctionalisation of the quinone substrate), examples of direct functionalisation methods are much less common. Despite the

arylation of *α,β*-unsaturated carbonyl compounds being commonly achieved by Heck coupling, benzoquinone has so far not been a suitable substrate for this methodology.

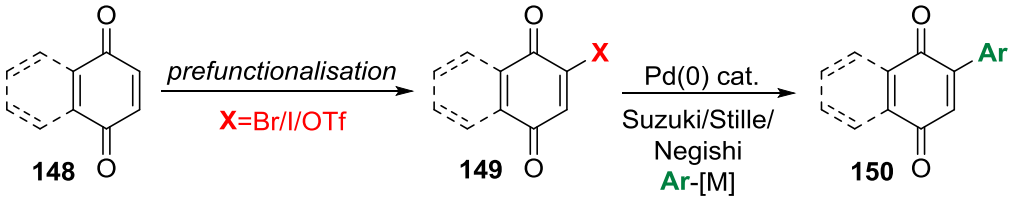
Indeed Felpin and co-workers recently highlighted the challenge in functionalising quinones *via* conventional Heck coupling processes:

> "Although almost every kind of olefin is compatible with the Heck process, benzoquinone-type partners are still reluctant to react under Heck protocols..."[17]

This review will highlight examples in the literature of the functionalisation of quinones using traditional Pd(0) cross-coupling methodology, alternative palladium-catalysed or palladium-mediated functionalisation examples, in addition to direct methods.

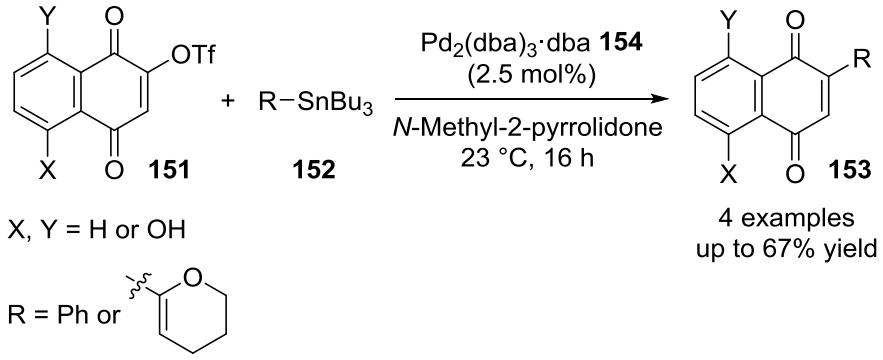
3.1.1 Functionalisation of benzoquinone by Pd(0) cross-coupling

Given the aforementioned challenges in applying classical C-C bond forming syntheses to benzoquinone, functionalisation has traditionally been accomplished *via* a multistep process. Prefunctionalisation of the quinone with Br, I or OTf, followed by a Stille, Negishi or Suzuki coupling reaction has proven a common method (Scheme 62) yet chemo- and regio-selectivity issues during halogenations pose a challenge.[18-20]



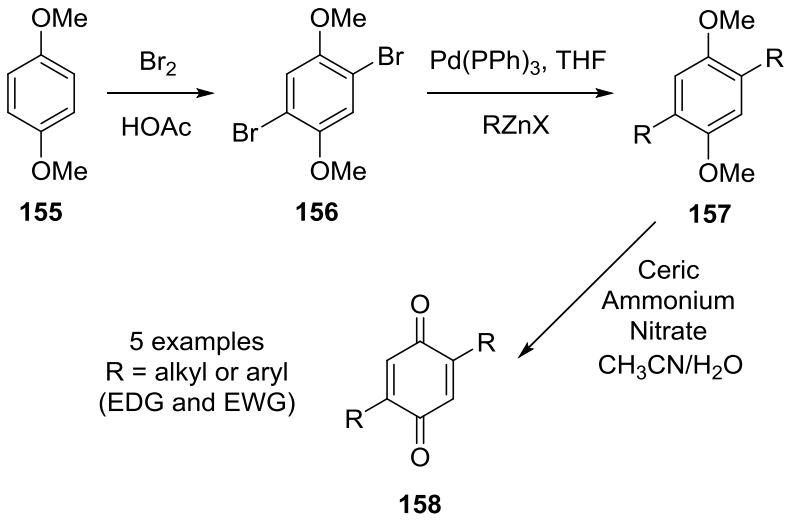
Scheme 62: Functionalisation of benzoquinone by Pd(0) cross-coupling

Echavarren and co-workers have published a number of reports on the Stille coupling of naphthoquinones with organostannanes.[21-24] The Stille coupling was adopted as part of synthetic routes to a number of biologically active compounds bearing the quinone moiety, or their precursors. As an alternative to using bromoquinone electrophiles, in 1997 Echavarren and co-workers also reported a Stille coupling with naphthoquinone triflates **151** and organostannanes **152** (Scheme 63).[22] Yields were moderate (up to 67%) with a range of substrate and organostannane combinations.



Scheme 63: Functionalisation of naphthoquinone by a Stille coupling reaction

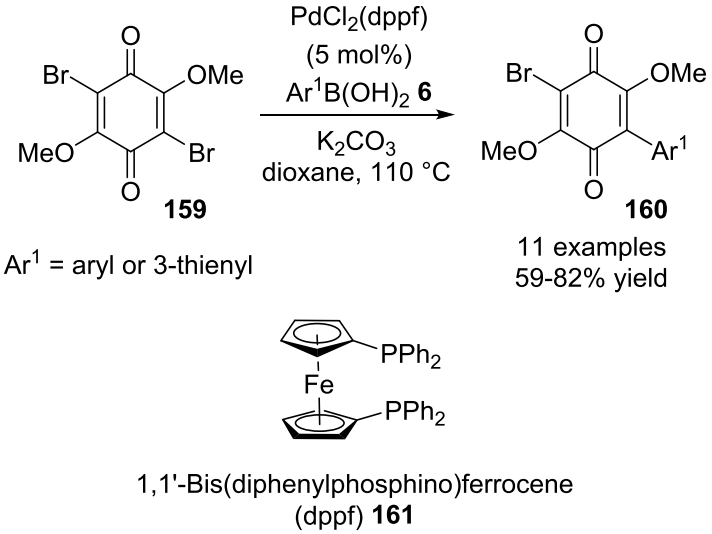
In 1998, Bäckvall and co-workers employed a double Negishi coupling to synthesise symmetrical 2,5-disubstituted quinones.[13] Prior to this, only one other example of the synthesis of such compounds had been reported.[25] The multistep approach to the target molecules used dimethoxybenzene **155** as a starting compound (Scheme 64). Bromination followed by Negishi coupling was carried out and the final quinone product **158** was formed by oxidative demethylation using ceric ammonium nitrate.



Scheme 64: Synthesis of 2,5-disubstituted benzoquinones *via* double Negishi coupling

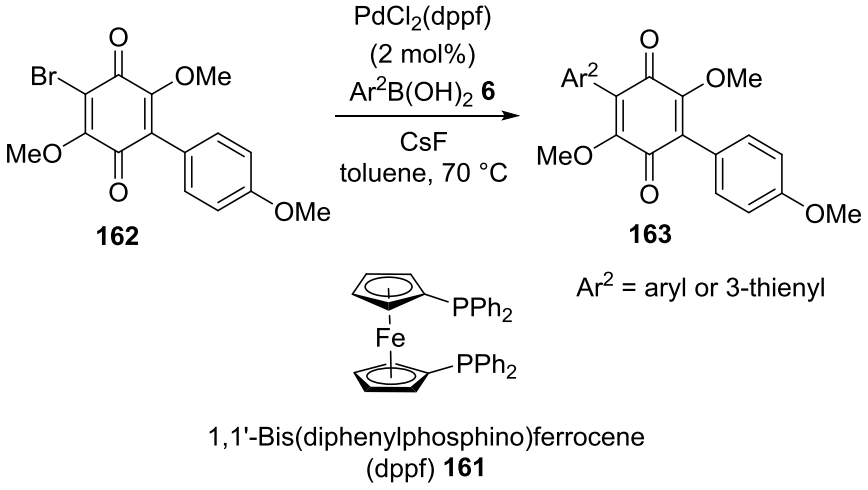
The Negishi coupling was carried out with various alkyl, vinyl and aryl zinc reagents to form the difunctionalised dimethoxybenzene **157** in 30-93% yield. A selection of these Negishi coupling products **157**, were then used for the final step to generate the difunctionalised benzoquinone product **158** in 65-95% yield.

Alternatively, Suzuki couplings have also been used as an effective synthetic route to functionalised quinones.[26, 27] In 2009, Hu and co-workers reported the functionalisation of 2,5-disubstituted benzoquinones **159** using two sequential Suzuki couplings in order to install two different aryl rings on the quinone core (Scheme 65).[28] The first arylation step to form **160** proceeded in up to 82% yield with a range of aryl boronic acids **6** with various steric and electronic properties.



Scheme 65: First Suzuki coupling step to synthesise 3,6-disubstituted 2,5-dioxybenzoquinones

The second Suzuki coupling was carried out using a mono-arylated benzoquinone (**162**, Scheme 66) from the first step and various aryl and heterocyclic boronic acids **6** as coupling partners. The reaction conditions were reoptimised to maximise yields and decent to excellent yields (59-82%) were obtained of the difunctionalised product **163**.



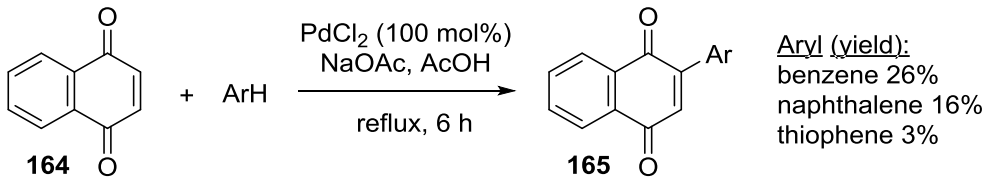
Scheme 66: Second Suzuki coupling step to synthesise 3,6-disubstituted 2,5-dioxybenzoquinones

Despite the aforementioned Pd(0) cross-coupling methods furnishing the desired functionalised quinones in decent yields, obviously the need to prefunctionalise the quinone substrate is a drawback to the methodology. Therefore, more direct methodology for functionalising quinones has obvious advantages.

3.1.2 Palladium-catalysed direct functionalisation of benzoquinone

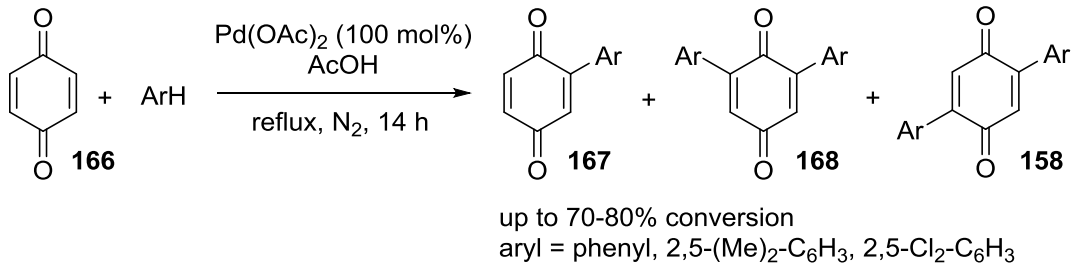
As previously mentioned, benzoquinone is more often used as an oxidant,[8-10] or a ligand[11-15] as opposed to the substrate in palladium catalysed reactions. Direct functionalisation of quinones using palladium is rare and restricted to a few examples, mainly with naphtho- and anthraquinone substrates as these substrates have a lower redox potential than benzoquinone.[4] The oxidative properties of benzoquinone[9] tend to hinder its ability to act as a substrate in these types of reactions. Additionally, whilst selectivity is not problematic for traditional Pd(0) cross-couplings (once the prefunctionalisation step has been completed), forming the mono- or difunctionalised products selectively has posed a challenge in some of the methodology discussed below.

In 1979, Pardhasaradhi and Choudary reported the use of stoichiometric palladium(II) to arylate 1,4-naphthoquinone **164** using benzene, naphthalene or thiophene as the arylating agents to yield the arylated naphthoquinone products **165**, albeit in low yields (3-26%, Scheme 67).[29]



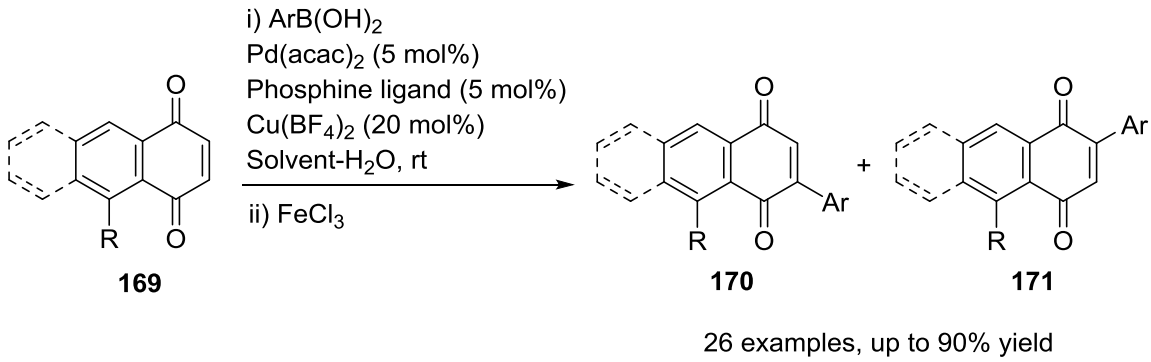
Scheme 67: Substitution of aryl moieties on naphthoquinone using stoichiometric palladium(II)

Itahara has also reported a direct functionalisation of quinones using stoichiometric $Pd(OAc)_2$ (Scheme 68).[30] The report which was published in 1985, details the oxidative coupling of both 1,4-benzoquinone and various naphthoquinones with a variety of aryl compounds. Whilst the study included limited examples of using benzoquinone as the substrate, 1,4- and 1,2-naphthoquinones were extensively studied and heterocyclic compounds (furan, thiophene, pyrrole and indole derivatives) were also used as (hetero)arylating agents. Yields were moderate to good yet when benzoquinone was used as a substrate selectivity was an issue, with a mixture of mono- (**167**) and difunctionalised (**158** and **168**) products obtained.[30] The proposed mechanism involved transmetallation of the aryl group onto palladium followed by migratory insertion of the palladium species onto the substrate. Reductive elimination yields the product and Pd(0).



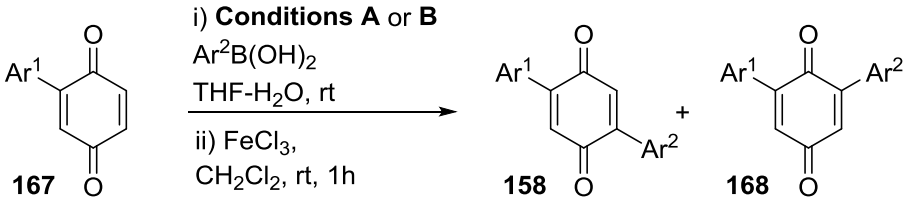
Scheme 68: Functionalisation of benzoquinone using stoichiometric $Pd(OAc)_2$

Csákÿ and co-workers have published a number of reports on the arylation of quinones. In 2009 they reported the successful arylation of naphtho- and anthraquinones catalysed by Pd(II) (Scheme 69).[31] The arylation formally comprised a conjugate addition reaction followed by an oxidation in a two step process. Regioselectivity was dependent on both the electronic nature of the substrate and also the reaction conditions used. Generally, a mixture of the 2- and 3-substituted products (**170** and **171**) was obtained but for a few examples, exclusive formation of one regioisomer over the other was observed.



Scheme 69: Arylation of naphtho- and anthraquinones using Pd(II)

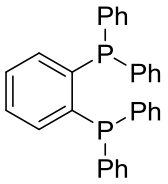
More recently, Csákÿ expanded work on the palladium(II) catalysed arylation of quinones by examining benzoquinone based substrates, using a similar catalytic protocol to earlier work (Table 17).[32] Functionalised benzoquinones (**167**) were used as the main substrates for the study, and a large part of the study comprised testing the efficacy of the products (**158** and **168**) as possible new drugs for the treatment of Alzheimer's disease.[32]



14 examples, up to 90% yield, 85:15 (**158:168**)

Conditions A (favour formation of 2,5 product):
$Pd(OCOCF_3)_2$ (5 mol%)
dppben (5.5 mol%), HBF_4 (1 equiv.)

Conditions (B favour formation of 2,6 product):
$Pd(OCOCF_3)_2$ (5 mol%)
AgOTf (1 equiv.)



1,2-bis(diphenylphosphino)benzene (dppben) **172**

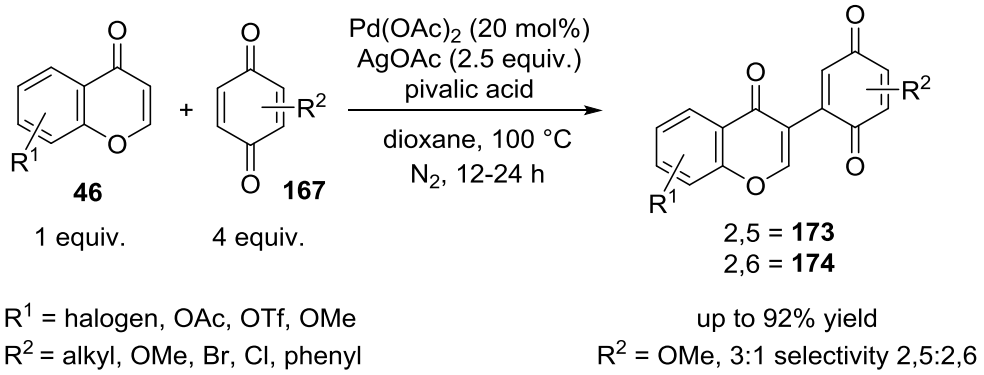
Entry	Conditions	Ar^1	Ar^2	Yield (%)	Ratio 158:168
1	A	Ph	Ph	90	85:15
2	A	Ph	*p*-CF_3-C_6H_4-	70	70:30
3	A	Ph	*p*-F-C_6H_4-	85	65:35
4	A	Ph	*p*-MeO-C_6H_4-	60	50:50
5	A	*p*-MeO-C_6H_4-	Ph	70	70:30
6	A	*p*-MeO-C_6H_4-	*p*-F-C_6H_4-	70	70:30
7	A	*p*-MeO-C_6H_4-	*p*-MeO-C_6H_4-	60	50:50
8	B	Ph	Ph	90	20:80
9	B	Ph	*p*-CF_3-C_6H_4-	70	35:65
10	B	Ph	*p*-F-C_6H_4-	60	30:70
11	B	Ph	*p*-MeO-C_6H_4-	60	40:60
12	B	*p*-MeO-C_6H_4-	Ph	70	40:60
13	B	*p*-MeO-C_6H_4-	*p*-F-C_6H_4-	65	30:70
14	B	*p*-MeO-C_6H_4-	*p*-MeO-C_6H_4-	60	40:60

Table 17: Pd(II)-catalysed bis-arylation of arylated benzoquinones

Up to 90% yields were obtained with a range of arylboronic acids (electron-donating and withdrawing). Regioselectivity depended on the conditions used; employing a bidentate phosphine ligand **172** (conditions A) gave the 2,5 di-arylated benzoquinone **158** as the major product (Table 17, Entries 1-7) whereas ligandless conditions B yielded predominantly the 2,6 di-arylated product **168** (Entries 8-14). Despite the

regioselectivity being tuned according to reaction conditions, a switch to solely one product over the other was not reported. Selectivities ranged from 50:50 in 60% overall yield (i.e. no selectivity, Table 17, Entry 7) to 85:15 2,5:2,6 product in 90% yield (Table 17, Entry 1) in the two step process.

In 2012, Moon and Hong reported a Pd(II)-catalysed direct route to isoflavone quinones (Scheme 70).[33] Benzoquinone and a range of chromones **46** were coupled in up to 92% yield. A number of substituted benzoquinones **167** were also screened and although yields were moderate to very good, regioselectivity was poor and mixtures of the 2,5 and 2,6 products (**173** and **174**) were obtained. The reaction was carried out under acidic conditions at 100 °C.



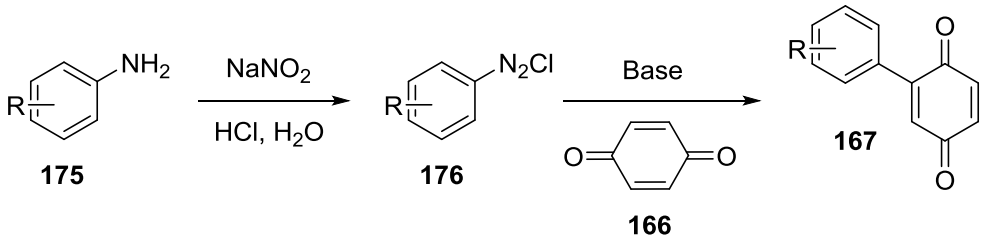
Scheme 70: Direct Pd(II)-catalysed cross-coupling of quinones and chromone

Moon and Hong proposed a mechanism whereby electrophilic palladation of the chromone takes place first followed by insertion of this palladated-species into the quinone. Subsequent reductive elimination forms the coupling product.

3.1.3 Direct functionalisation of quinones using non palladium-catalysed methods

The Meerwein arylation has proven to be a popular method for direct functionalisation of quinones. In 1934, Kvalnes reported the arylation of benzoquinone using a wide variety of aryl diazonium salts.[34] Since this initial report, the Meerwein arylation has become one of the more popular methods to functionalise quinones given that direct functionalisation is possible using this methodology and no prefunctionalisation of the quinone substrate is necessary (Scheme 71).[17, 35, 36] However, the use of aryldiazonium

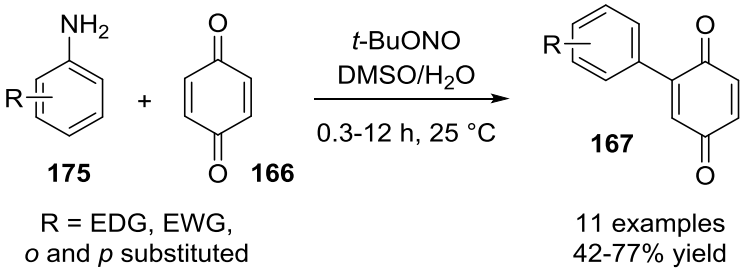
salts poses problems given that they can be unstable, explosive and difficult to synthesise.[17]



Scheme 71: Meerwein arylation to functionalise benzoquinone

Felpin and co-workers have recently reported the arylation of benzoquinone using Meerwein arylation methodology.[16, 36] However, handling of hazardous aryldiazonium salts is avoided by using the corresponding anilines. Following the generation of the aryldiazonium salts *in situ* from the aniline starting materials, a Meerwein arylation is carried out using benzoquinone as a substrate.[17, 37]

In the original work by Felpin and co-workers (2012), the direct arylation of benzoquinone **166** was carried out in the presence of *tert*-butyl nitrite with a range of different anilines **175** bearing electron-donating and withdrawing groups in up to 77% yield (Scheme 72).[37] This methodology was advantageous over the traditional Meerwein arylation route as the reaction proceeded under neutral conditions without the need for any acid or base. From experimental observations, a free-radical pathway was proposed for the mechanism and it was observed that reaction rates were shorter and yields higher when electron-withdrawing anilines were employed.



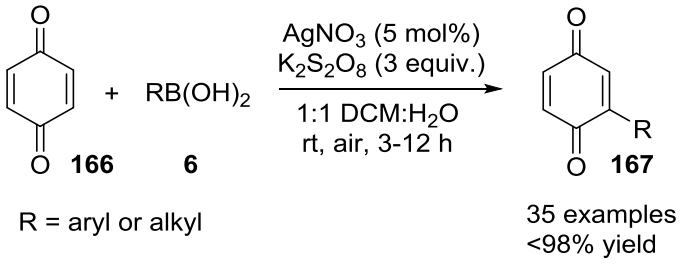
Scheme 72: Direct arylation of benzoquinone using anilines

In 2013, Felpin and co-workers reported further studies into the C-H arylation of benzoquinone with anilines and published the first example of a Meerwein arylation using a heterogeneous catalyst.[17] Studies found that using graphite-supported copper

oxide nanoparticles, the reaction efficiency could be improved and a wider variety of functional groups could be tolerated than in previous studies.

As this review has highlighted, quinones are traditionally functionalised *via* multistep processes requiring prefunctionalisation of the quinone moiety followed by traditional cross-couplings or the use of hazardous diazonium salts to carry out Meerwein arylations. Recently however, direct methods have been reported by Baran and co-workers amongst others which employ less hazardous reagents in direct functionalisation protocols, thus providing a more facile route to functionalised quinones.

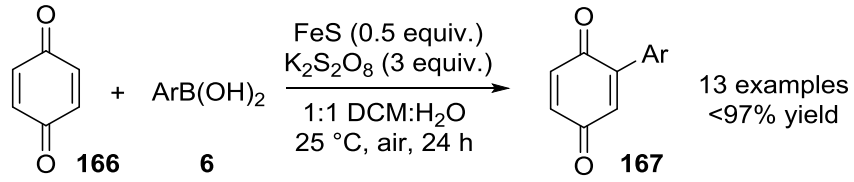
In 2011, Baran and co-workers reported a silver-catalysed direct functionalisation of benzoquinones to form the corresponding monofunctionalised products (Scheme 73).[38] By using boronic acids and a strong oxidant ($K_2S_2O_8$), a radical mechanism was proposed for the reaction which proceeded under mild conditions and with a range of aryl and alkyl boronic acids **6** to furnish the monofunctionalised products **167** in up to 98% yield. Despite this example marking significant progress in developing methodology for the direct functionalisation of benzoquinone, the use of a strong oxidant limits the scope of the reaction.[39] Additionally, whilst aryl halides are tolerated, no examples of heterocycle or alkene functionalisations are reported. Also, very electron-withdrawing aryl and very hindered alkyl boronic acids in addition to oxidisable functional groups are not tolerated using this method.[38] A few select examples of substituted benzoquinone substrates (bearing alkyl, methoxy and chloro substitutents) and naphthoquinone were included in a small quinone substrate screen with *para*-methylphenyl boronic acid. Whilst yields were good (up to 87%), in cases where regioselectivity could be an issue, the selectivity was indeed poor.



Scheme 73: Silver nitrate catalysed CH functionalisation of quinones with boronic acids

The application of this methodology was subsequently exhibited in a number of reports published by Baran and co-workers showing the versatility of the functionalisation reaction in the synthesis of various natural products.[40-42]

In 2012, an iron-mediated direct arylation of quinones with arylboronic acids was reported by Yu and co-workers (Scheme 74).[43] Using iron sulfide (a cheaper alternative to silver nitrate) as the catalyst (albeit 0.5 equivalents) and potassium persulfate as the oxidant, various aryl boronic acids **6** with a range of steric and electronic properties were coupled with benzoquinone **166** in up to 97% yield of the monofunctionalised product **167**. Yu and co-workers proposed that the coupling may proceed through a radical mechanism, similar to Baran's mechanistic proposal. Additionally, a number of substituted benzoquinones bearing alkyl, chloro and methoxy substituents in addition to naphthoquinone were used as substrates and yielded the desired coupling products although yields were significantly reduced compared to when unsubstituted benzoquinone **166** was used as a substrate.



Scheme 74: Iron-mediated direct arylation of benzoquinone with aryl boronic acids

Since the aforementioned reports of direct functionalisation of benzoquinone by Baran and Yu, other examples of direct functionalisation of quinones have come to the fore using similar methodologies.[44-46] Using analogous conditions to Baran, Malayappasamy and co-workers adopted the $AgNO_3/K_2S_2O_8$ catalytic system to alkylate benzoquinones using cyclopropanols.[44] Also, Komeyama and co-workers used a $FeSO_4/K_2S_2O_8$ catalytic system to arylate benzoquinone using arylboronic acids and trifluoroborate salts.[45]

3.1.4 Conclusion

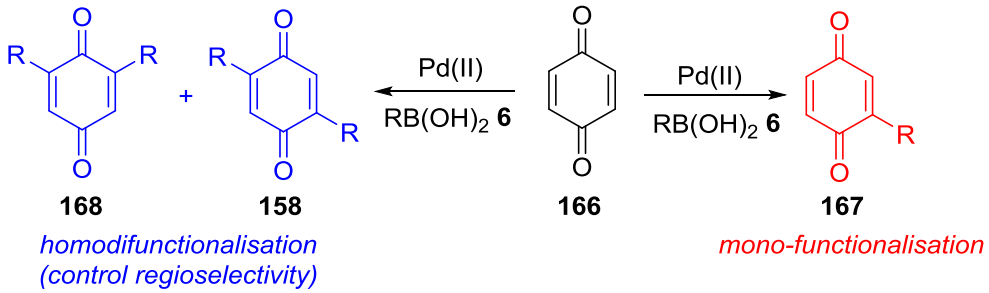
Despite the emergence of a number of reports on the functionalisation of quinones in recent years, there is still plenty of scope for investigation in this area. When traditional Pd(0) cross-coupling methodologies are used, benzoquinone acting as an oxidant rather than a substrate is a major challenge. Even when reactions can be carried out using benzoquinone as the substrate, for instance using Pd(II) catalysts, control of mono- *versus* difunctionalisation and selectivity of the latter continues to pose a challenge.

Although recent advances have been made following Baran's seminal work in 2011 (using silver- and iron-based catalysts), limitations still exist; the reactions are limited to mono-arylations and very electron-withdrawing aryls, heterocycles, alkenes and oxidisable functional groups are not tolerated. Therefore, improvements to substrate scope, functional group tolerance and control of mono- *versus* difunctionalisation would be advantageous.

3.2 Project aim

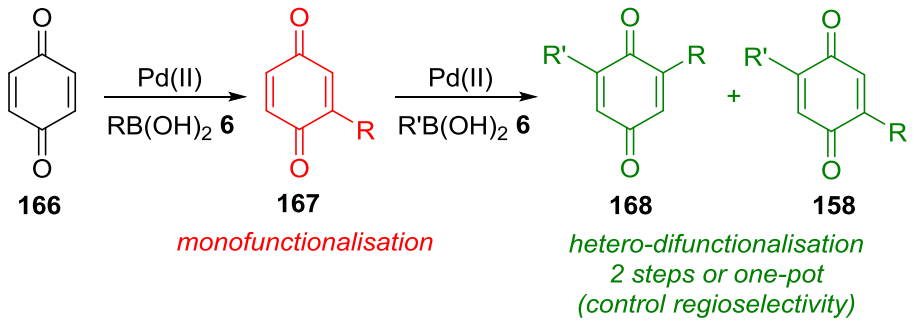
Extensive investigations have been carried out within the Lee group on Pd(II)-catalysed conjugate addition and oxidative Heck reactions (for example see chapter 2).[47, 48] During the course of investigations into oxidative Heck reactions on challenging substrates such as cyclic enones, the question was raised as to whether our cationic Pd(II) system developed previously, could be applied to benzoquinone.

In this project, we aim to develop a practical, direct C-H functionalisation of benzoquinone, which can be controlled to give mono- (**167**) or difunctionalised (**158** or **168**) products (Scheme 75). In particular, we hope to develop a method whereby a wide variety of functional groups (R) are tolerated, including both electron-donating and electron-withdrawing aryls, heteroaryls, alkyls and alkenes, given that current approaches have a limited substrate scope.



Scheme 75: Project aim – Pd(II)-catalysed mono- and difunctionalisation of benzoquinone

Finally, we would also like to develop a direct method for functionalising benzoquinone with two different groups, ideally in a one-pot procedure (Scheme 76). Such a methodology would constitute an advancement in the field and allow benzoquinones to be functionalised practically and readily in one step.



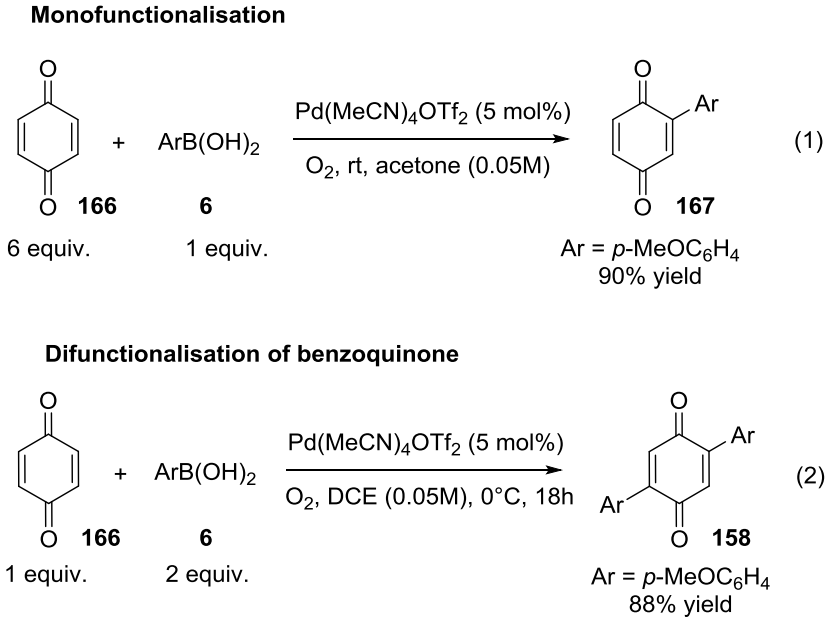
Scheme 76: Project aim – Pd(II)-catalysed hetero-difunctionalisation of benzoquinone*

*For numbering purposes, 2,5 difunctionalised benzoquinones will be numbered **158** and 2,6 difunctionalised benzoquinones will be numbered **168** throughout this thesis regardless of whether they are homo- or heterodifunctionalised. In order to identify the functional groups, letters will be added after the appropriate number.

3.3 Monofunctionalisation of benzoquinone

3.3.1 Initial optimisation studies

Initial studies on the functionalisation of benzoquinone were carried out by J. Jordan-Hore. The cationic Pd(II) catalyst [$Pd(OTf)_2$] used within the Lee group for previous work was initially probed to see if it would be effective in catalysing the functionalisation of benzoquinone with aryl boronic acids as the coupling partner. Optimised conditions were found for both mono- and difunctionalisation by J. Jordan-Hore (Scheme 77). These were then used in initial work to examine the scope of the reaction.



Scheme 77: Initial optimised reaction conditions (by J. Jordan-Hore) for the functionalisation of benzoquinone

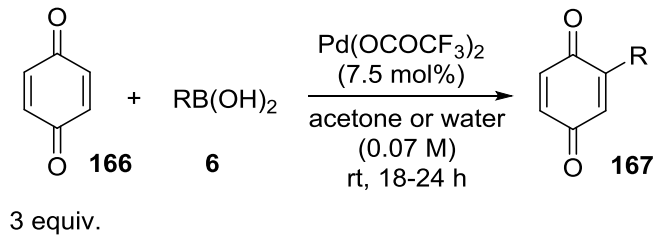
Unfortunately, initial work carried out by the author using these optimised reaction conditions was hampered by irreproducible results and poor yields. The conditions gave a complex mixture of products, particularly for the difunctionalisation reactions, and yields were inconsistent. For instance, on repeating the original promising monofunctionalisation result (Scheme 77, Equation 1), a 32% yield of monofunctionalisation product **167** was obtained compared to the initial result where 90% yield was observed. On turning our attention to the difunctionalisation reactions, the maximum yield obtained of product **158** was 58% compared to 88% in initial optimisation work (Scheme 77, Equation 2). As a result of our findings, extensive

optimisation studies were continued (by J. Jordan-Hore) examining catalyst, solvent and temperature resulted in suitable reaction conditions being found. The less active catalyst $Pd(OCOCF_3)_2$ was found to be effective, coupled with acetone or water as solvents and reactions became more reproducible. In retrospect, part of the problems encountered could be attributed to benzoquinone acting as both the substrate and an oxidant. Additionally, the mono- and/or difunctionalised products formed were also likely to be acting as oxidants or further reacting thus giving the poor, irreproducible yields experienced and an indiscriminate reaction outcome.

Pleasingly, the newly optimised reaction conditions gave good yields of the desired products, in air and at room temperature (Scheme 78). Additionally, the appropriate boronic acid can be used straight from the bottle in this case rather than being dehydrated to boroxine form, or recrystallised to form the boronic acid, which was a necessity in previous work in order to achieve good yields.[48]

Another challenge during optimisation was the competing homodifunctionalisation reaction. However, by optimising the stoichiometry of reagents it was possible to suppress the difunctionalisation reaction so that the monofunctionalised product was formed exclusively.

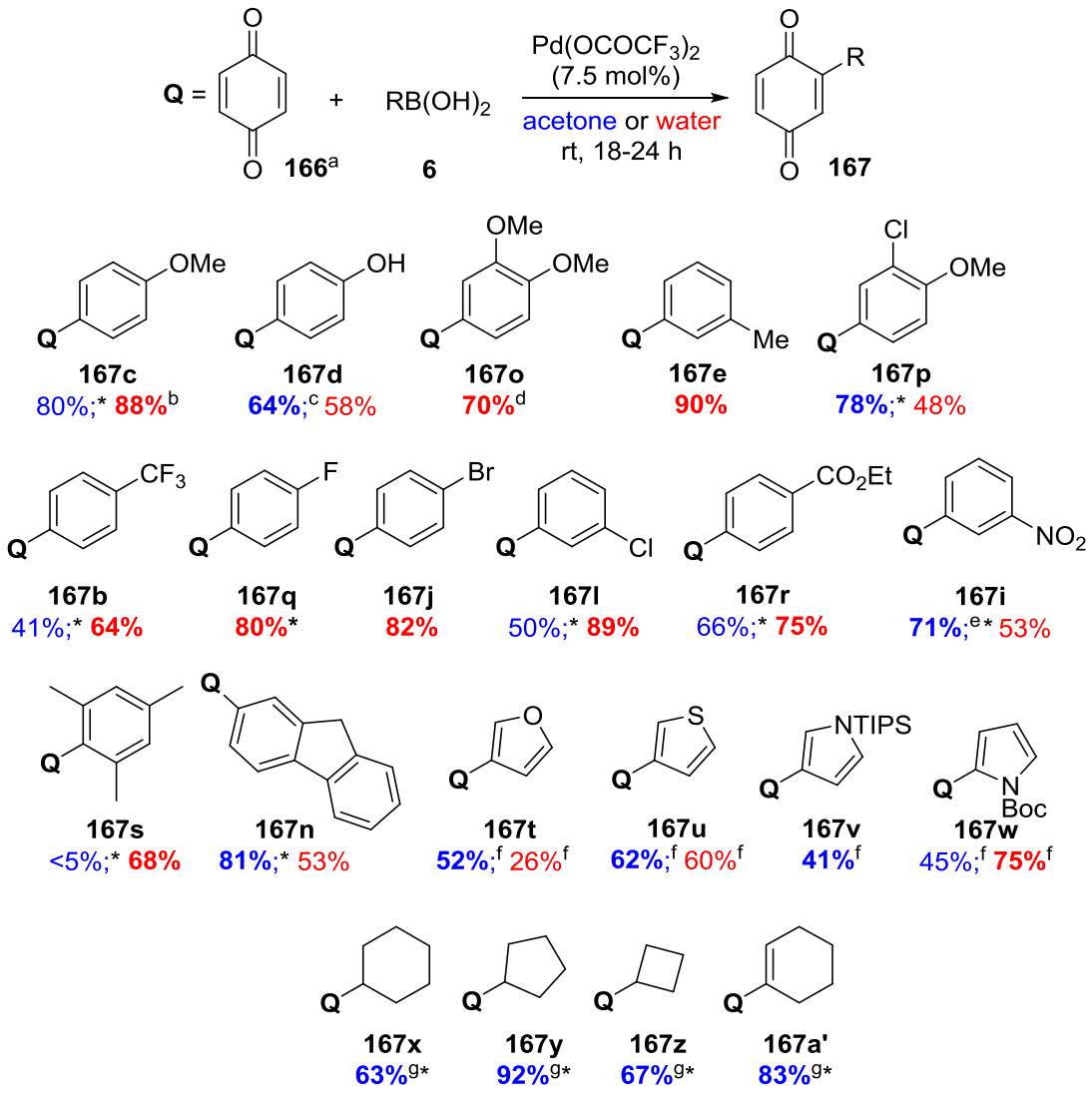
In addition to being the substrate, benzoquinone was found to act as an oxidant also (see Scheme 88 for possible reaction pathways and roles of the oxidant). Taking these factors into account, three equivalents of benzoquinone to one of boronic acid were found to be optimal for the monofunctionalisation reaction (Scheme 78).



Scheme 78: Optimised reaction conditions for the Pd(II)-catalysed mono functionalisation of benzoquinone

3.3.2 Boronic acid screen

Using the optimised conditions for the monofunctionalisation reaction, a boronic acid screen was conducted (Scheme 79). Given that initial optimisation work had demonstrated that the reaction could be carried out in both water and acetone, all monofunctionalisation reactions shown were carried out in both solvents. Yields in blue indicate reactions carried out in acetone, and those in red correspond to using water as the solvent. Where only one value is given, the other solvent gave poor conversion and the product was not isolated.



[a]BQ (3 equiv.), $RB(OH)_2$ (1 equiv.). [b]87% with 1 mol% cat. [c]6 Equiv. BQ used. [d]Gram scale reaction also 70%. [e]50 °C, 48 h. [f]40 h. [g]40 °C, 48 h, 2 × 7.5 mol% catalyst. *Reaction carried out by J. Jordan-Hore.

Scheme 79: Boronic acid screen

Results from the boronic acid screen showed that the reaction is tolerant of a range of boronic acids with various steric and electronic properties. Electron-donating boronic acids gave good to excellent yields in water and acetone (*p*-OMe-C_6H_4-, *m,p*-$(OMe)_2$-C_6H_3- and *m*-Me-C_6H_4-, **167c, 167o** and **167e**). *Para*-OH-C_6H_4- boronic acid in acetone was found to be incredibly reactive and J. Jordan-Hore observed formation of the homodifunctionalised product under the standard conditions. However, this reaction was suppressed by using an additional 3 equivalents of benzoquinone to give the desired monofunctionalised product in 64% yield (**167d**). Electron-withdrawing boronic acids also give good yields (*p*-CF_3-C_6H_4- **167b**, *p*-F-C_6H_4- **167q**, *m*-Cl-C_6H_4- **167l** and *p*-CO_2Et-C_6H_4- **167r**) despite the electronics of these boronic acids making transmetallation more challenging. *Meta*-NO_2-C_6H_4- boronic acid performed well but needed a longer reaction time and higher temperature to yield product **167i**. Aryl boronic acids bearing groups with differing electronic properties also fare well (*m*-Cl-*p*-OMe-C_6H_4-, **167p**) in both solvents and sterically hindered mesityl boronic acid performs well in water but gives trace product in acetone (**167s**).

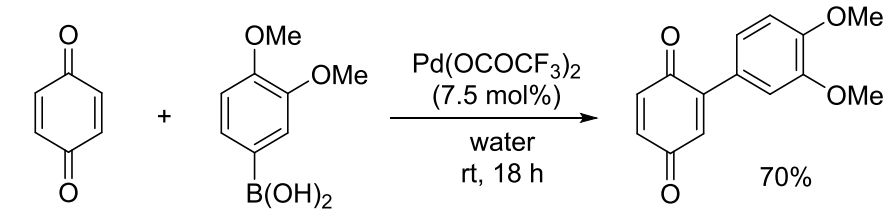
The reaction also tolerates boronic acids with readily oxidisable positions such as 2-fluorene (**167n**, which would not be compatible with other methods using strong oxidants[39]) and is tolerant of carbon-bromine bonds (*p*-Br-C_6H_4 boronic acid, **167j**), which may be expected to be problematic given their susceptibility to insertion of Pd(0). Additionally, a cyclic alkenyl boronic acid (**167a'**) is also tolerated, which, given the propensity of benzoquinone to undergo Diels-Alder type reactions (and that during initial optimisation acyclic alkene boronic acids produced a complex mixture of products, presumably due to further reactions of the product), also demonstrates the tolerance of the reaction to a wide range of functional groups.

Despite their known propensity to undergo protodeboronation readily,[49, 50] heterocyclic boronic acids were also investigated and were suited to our conditions, albeit needing a longer reaction time of 40 hours for the reaction to go to completion. 3-Thienyl boronic acid performed well in both water and acetone (**167u**). 3-Furan boronic acid also gave the desired monofunctionalised product (**167t**) although the yield was poorer than its sulphur counterpart. Pyrrole boronic acids also formed product but yields were mixed and depended on the protecting group and solvent used (**167v** and **167w**). Considering the challenge presented in monofunctionalising benzoquinone with heterocycles and the absence of examples in the literature of this transformation, our results demonstrate a significant advancement in this area.

During initial investigations carried out by J. Jordan-Hore, acyclic alkyl boronic acids were found to be susceptible to *β*-hydride elimination. However, gratifyingly, cycloalkyl boronic acids are able to functionalise benzoquinone with slight alterations to the standard reaction conditions. By using a slightly higher reaction temperature than that used for aryl boronic acids and leaving the reaction for 2 days with an additional portion of catalyst added after 24 hours, moderate (cyclohexyl **167x** and cyclobutyl **167z** boronic acids) to excellent (cyclopentyl boronic acid, **167y**) yields are obtained in acetone as the solvent.

It is not clear why some boronic acids fare better in water as a solvent whilst others give higher yields in acetone. There does not seem to be an obvious trend in results which can be attributed to the solvent used. However, as a general rule, aryl boronic acids react well in water (results in red) and often give higher yields in this solvent rather than acetone (results in blue). On the other hand, heterocyclic, cycloalkyl and cycloalkenyl boronic acids give higher yields in acetone, and in some cases (such as for the cycloalkyl and alkenyl boronic acids), do not yield product when water is used as a solvent.

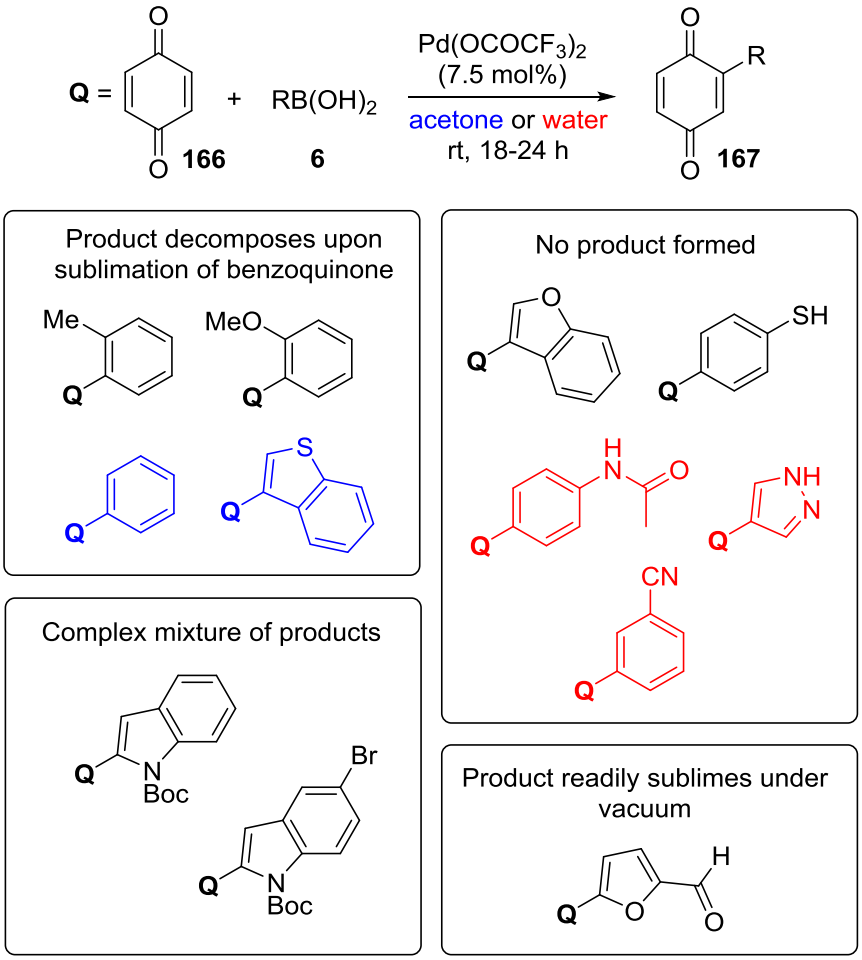
During the course of our studies we also wanted to investigate if our reaction could be scaled up and still give good yields. Using *m,p*-$(OMe)_2$-C_6H_3- boronic acid **6o**, we carried out a gram scale reaction which gratifyingly gave a comparable yield to that obtained when the reaction was carried out using the standard scale for our optimised reaction conditions (Scheme 80).



Scheme 80: Gram-scale reaction of benzoquinone with *m,p*-$(OMe)_2$-C_6H_3-boronic acid

Despite our success in functionalising benzoquinone with a wide range of boronic acids, regrettably, we found that some boronic acids were not suited to our reaction conditions or methodology. Boronic acids which did not give the desired product are shown below (Scheme 81). Boronic acids which were only probed in either acetone or water are

shown in blue or red respectively. Those which were tried in both solvents are shown in black.



Scheme 81: Products which were not isolated during the boronic acid screen

During initial optimisation studies and the boronic acid screen, purification posed a challenge as some products were found to coelute with the excess benzoquinone used in the reaction. For reactions where this occurred, this was overcome by isolating the product and benzoquinone mixture as a solid/oil and subliming the benzoquinone using a Kugelrohr distillation apparatus, rendering the pure product. This method was generally successful. However, for a number of boronic acids, decomposition of the product, or sublimation of the product itself occurred during this process and therefore purification of pure product was not possible. This occurred with phenyl, *o*-OMe-C_6H_4-, *o*-Me-C_6H_4-, 5-formyl-2-furan- and benzo[*b*]thiophene-2-boronic acids.

Other boronic acids which unfortunately did not give the desired product include various nitrogen heterocycles. Protected indoles (*N*-Boc-indole-2-boronic acid and *N*-Boc-5-bromo-2-indolyl boronic acid) tend to give a complex mixture of products (by

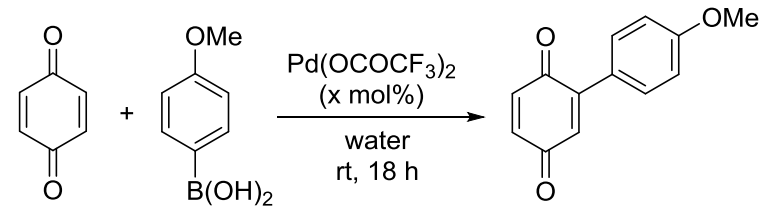
TLC analysis). As previously mentioned, these boronic acids have a tendency to undergo homocoupling and protodeboronation reactions and therefore products from these reactions may well have been formed rather than our desired monofunctionalised products. Unprotected nitrogen heterocycles (1*H*-pyrazole-4-boronic acid) and nitrogen bearing boronic acids (*m*-cyano-C_6H_4-, *p*-acetamido-C_6H_4-) do not react at all, presumably due to the nitrogen lone pair coordinating to palladium and thus deactivating the catalyst. Additionally, *p*-HS-C_6H_4- and benzo[*b*]furan-2-boronic acids also do not yield product.

Our interest was primarily in finding boronic acids which could be used in both water and acetone to functionalise benzoquinone. Therefore, for some of the boronic acids mentioned above which did not give the desired product, the reaction was only carried out in one of the aforementioned solvents. Where no yield was obtained, or decomposition of the product occurred for instance, as a rule the boronic acid was not probed in the other solvent.

3.3.3 Reducing catalyst loading

As a result of initial optimisation studies carried out by J. Jordan-Hore, the standard procedure for the monofunctionalisation of benzoquinone uses 7.5 mol% catalyst loading. This was necessary for more challenging boronic acids such as heterocycles and cycloalkyl and alkenyl boronic acids in order to obtain reasonable to good yields of the desired product.

However, we were interested to compare a range of catalyst loadings to see if less catalyst would still give reasonable yields of product, when a more active electron-donating boronic acid is used (Table 18). Pleasingly, results indicate that more active boronic acids still react well under lower catalyst loadings. On reducing the catalyst loading to only 1 mol%, and using *p*-OMe-C_6H_4-boronic acid for this screen, the yield was comparable to that obtained in monofunctionalisation reactions (Entries 1 and 2; 87% yield with 1 mol% catalyst compared to 88% with 7.5 mol%). On reducing the loading further to 0.1 mol% (Table 18, Entry 3) we did however observe a drop in yield to 37%.



166 **6** **167c**

3 equiv.

Entry	Catalyst loading (mol%)	Yield (%)
1	7.5	88
2	1.0	87
3	0.1	37

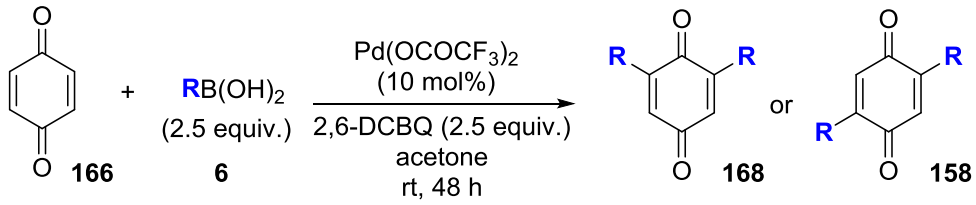
Table 18: Reducing catalyst loading in the monofunctionalisation of benzoquinone

3.4 Homodifunctionalisation of benzoquinone

3.4.1 Homodifunctionalisation – initial optimisation

Given that current methods to difunctionalise benzoquinone require multistep syntheses (see section 3.1),[13, 28, 32] we were keen to investigate whether our methodology could be applied to carry out a one step homodifunctionalisation of benzoquinone. Optimisation studies were carried out by J. Jordan-Hore using the monofunctionalisation reaction conditions as a starting point. Given that an excess of benzoquinone was used in the monofunctionalisation reactions as an oxidant and to prevent difunctionalisation products being formed, this was obviously not an option for difunctionalisation and an alternative oxidant was needed for this reaction. Extensive screening of alternative oxidants for this reaction was carried out by J. Jordan-Hore[51] and the choice of oxidant was also crucial to ensure that the monofunctionalised product would not itself act as an oxidant in the reaction. This was a particular issue in initial optimisation studies.

The oxidant screen found that 2,6-dichloro-1,4-benzoquinone was a suitable oxidant and a catalyst loading of 10 mol% of $Pd(OCOCF_3)_2$ was optimal, in addition to using a slight excess of boronic acid, which was used straight from the bottle, similar to the monofunctionalisation reactions (Scheme 82). Pleasingly, the homodifunctionalisation reaction proceeded well at room temperature over 2 days.



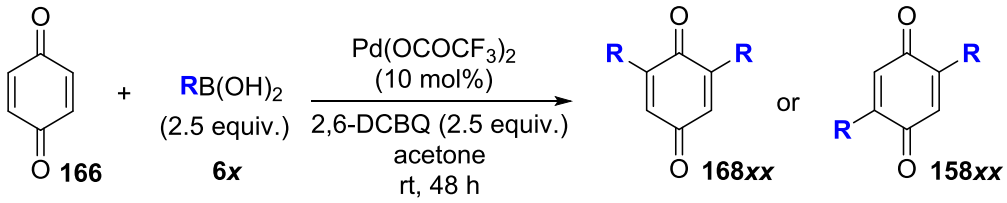
Scheme 82: Optimised conditions for the homodifunctionalisation of benzoquinone

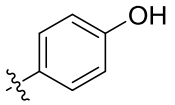
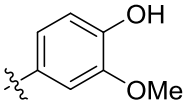
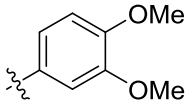
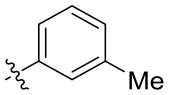
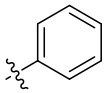
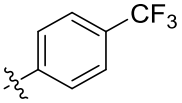
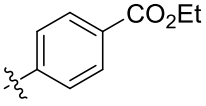
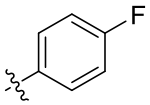
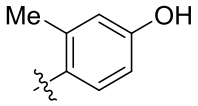
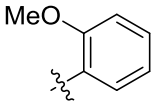
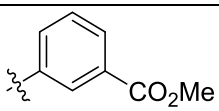
3.4.2 Boronic acid screen

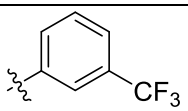
With the optimal reaction conditions in hand, we then conducted a boronic acid screen (Table 19).

The products formed in the homodifunctionalisation reaction were the 2,5 and 2,6 disubstituted products. Often the isomers had very similar R_f values and initial purification posed a challenge. However, during the course of our studies we observed a trend in the formation of these isomers; electron-rich boronic acids preferentially formed the 2,6 substituted product whereas the 2,5 substituted product was the major isomer for electron-poor boronic acids. Given the current lack of methodology to selectively functionalise benzoquinone, being able to control formation of the 2,5 or 2,6 product preferentially using the electronics of the boronic acid as a tool is certainly advantageous and an advancement in this area.

The homodifunctionalisation reaction proceeded in good yields with a range of boronic acids with differing steric and electronic properties and was tolerant of various functional groups (Table 19).



Entry	RB(OH)$_2$ (R =)	Yield 168 (%)[a]	Yield 158 (%)[a]
1	 **6d**	**168dd** 71	**158dd** <5
2	 **6b'**	**168b'b'** 73	trace
3	 **6o**	**168oo** 58	ND
4	 **6e**	**168ee** 53	**158ee** 28
5	 **6a**	**168aa** 29	**158aa** 44
6[b]	 **6b**	-	**158bb** 51
7[b,c,d,e]	 **6r**	-	**158rr** 25
8[b,f]	 **6q**	-	**158qq** 13
9[g]	 **6c'**	41% combined yield (1:1 ratio **168c'c':158c'c'**)	
10	 **6d'**	**168d'd'** 25	**158d'd'** 28
11[b,c,d,g]	 **6h**	75% combined yield (3:2 ratio **168hh:158hh**)	

12[b,d,f]	**6e'** 	60% combined yield (1:1 ratio **168e'e':158e'e'**)

[a]Isolated yields. [b]35 °C. [c]Additional catalyst and boronic acid added. [d]Treated with $FeCl_3$ and/or DCBQ at the end of reaction. [e]Product only moderately stable. [f]Additional 2,6-DCBQ, catalyst and boronic acid added. [g]Isomers not fully separable.

Table 19: Homodifunctionalisation of benzoquinone boronic acid screen

As expected, electron-rich boronic acids reacted well, giving very good yields and excellent selectivity, forming the 2,6 isomer preferentially (*p*-OH-C_6H_4-, *m*-OMe-*p*-OH-C_6H_3-, *m*,*p*-OMe-C_6H_3-, Entries 1-3). As the substituents on the phenyl ring of each boronic acid became steadily less electron-donating (*m*-tolyl, Entry 4) and neutral (phenyl, Entry 5), the ratio of 2,6:2,5 isomers reduced, but the combined yields of both isomers remained very good.

For electron-withdrawing boronic acids (*p*-CF_3-C_6H_4-, *p*-CO_2Et-C_6H_4- and *p*-F-C_6H_4-, Entries 6-8) the selectivity switched to formation of the 2,5 isomer preferentially. An exception to this observed trend is the selectivity observed with the less electron-withdrawing *m*-CO_2Me-C_6H_4- and *m*-CF_3-C_6H_4- boronic acids (Entries 11 and 12) which gave no, or very little selectivity. The electron-withdrawing boronic acids were less reactive than their electron-rich counterparts and initial reactions using the standard conditions often gave poor yields. By increasing the temperature to 35 °C and in some cases adding additional portions of boronic acid, DCBQ and catalyst, yields were improved but still somewhat reduced compared to when electron-rich boronic acids are used.

In addition to electronic effects, steric effects also seemed to play their part in reducing yields and selectivity. Presence of an *ortho* substitutent (*o*-Me-*p*-OH-C_6H_3- and *o*-OMe-C_6H_4-, Entries 9 and 10) reduced yields and also the selectivity of the reaction. Whilst excellent selectivity and yield are obtained when *p*-OH-C_6H_4-boronic acid is used, *o*-Me-*p*-OH-C_6H_3- boronic acid, shows no selectivity and the combined yield of both isomers drops to 41% (Entry 1 *versus* Entry 9).

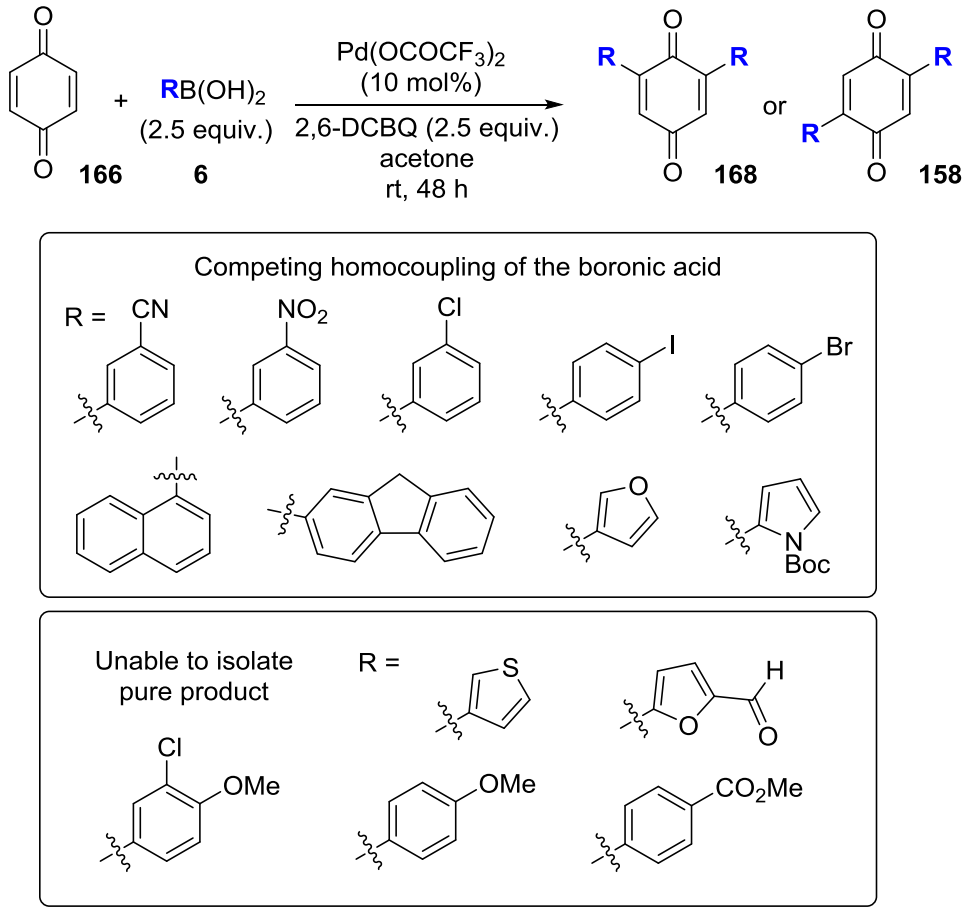
With regards to the reduction in yield with electron-withdrawing boronic acids, a number of reasons for this became evident. Firstly, from NMR and TLC analysis, the hydroquinone species of the product was believed to be present in those reactions where

yields were poor. This could be attributed to the product competing with DCBQ as an oxidant in the reaction. Additionally, the homodifunctionalised products formed from electron-poor, or heterocyclic boronic acids seemed to be less stable than their electron-donating counterparts and this would have also contributed to the reduced yields observed.

In order to maximise yields obtained for reactions using electron-poor or heterocyclic boronic acids, a number of possible solutions were sought. Each reaction with electron-withdrawing boronic acids needed to be treated slightly differently depending on the problems identified when carrying out initial reactions. For *p*-CF_3-C_6H_4-boronic acid, an elevated temperature of 35 °C was found to be sufficient to give a reasonable yield of exclusively the 2,5 product (Entry 6). This increase in temperature was applied to reactions with all the other electron-withdrawing boronic acids, but yields still remained low and therefore additional changes to the optimised reaction conditions were needed to give appreciable amounts of product in these reactions.

In order to increase yields, a portionwise addition approach was adopted where additional portions of catalyst, boronic acid and in some cases 2,6-DCBQ were added after 24 h in order to push the reaction to completion and minimise the amount of reduced product formed (*p*-CO_2Et-C_6H_4-, *p*-F-C_6H_4-, *m*-CO_2Me-C_6H_4- and *m*-CF_3-C_6H_4-, Entries 7, 8, 11 and 12). In some cases this was still deemed insufficient and additional oxidant was added for an hour at the end of the reaction, and/or to the column wash after purification in order to oxidise any reduced product. Further purification of this solution then yielded more of the desired product (see experimental section for further details). Iron(III) chloride was found to be an effective oxidant and was used in these cases instead of DCBQ. In particularly challenging cases, such as for *m*-CF_3-C_6H_4-boronic acid, both DCBQ and $FeCl_3$ were used in order to maximise yield (Entry 12).

Despite the aforementioned problems being solved to give reasonable yields of products with electron-withdrawing substituents, disappointingly, a number of additional boronic acids were tried which did not yield product (Scheme 83).



Scheme 83: Homodifunctionalised products which were not isolated

For many electron-poor boronic acids, no homodifunctionalised product was evident from TLC analysis during the reaction, but instead a complex mixture of products. Even an elevated temperature of 35 °C for some of the reactions did not yield product. Competing homocoupling of the boronic acid to form the dimer was certainly a problem in many of these reactions. Boronic acids where this was the case include: *N*-Boc-2-pyrrole, *m*-CN-C_6H_4-, *m*-NO_2-C_6H_4-, *m*-Cl-C_6H_4-, *p*-I-C_6H_4-, *p*-Br-C_6H_4-, 3-furan, 2-fluorene and 1-naphthyl boronic acids.

Unfortunately, heterocyclic boronic acids were not tolerated well by the reaction conditions and whilst the reaction with 3-thiophene boronic acid did give 2,5 and 2,6 isomers, purification posed a challenge coupled with instability of the products.

An additional challenge was purification of reactions where coelution of the product, often with either benzoquinone, 2,6-DCBQ or its reduced form, was an issue and therefore pure product could not be isolated. This was the case with a number of

substrates including *p*-OMe-C_6H_4-, *m*-Cl-*p*-OMe-C_6H_4-, 5-formyl-2-furan and *p*-CO_2Me-C_6H_4- boronic acids.

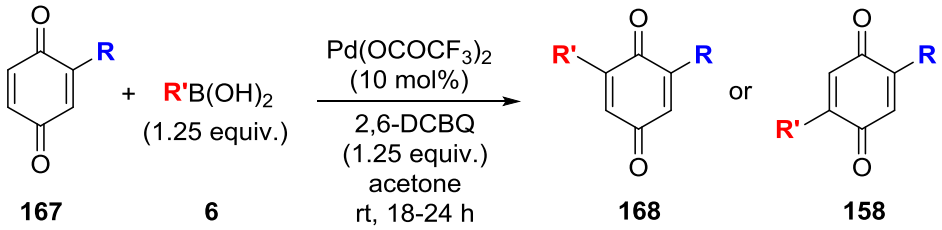
A potential option for future work in this area would be to examine more closely the reasons for those reactions which did not yield product. Evidently, due to the products acting as oxidants in addition to being unstable, the homodifunctionalisation using *electron-poor* boronic acids could be improved in order to increase yields. Where the use of DCBQ was problematic, investigations into alternative oxidants (aside from $FeCl_3$) could be pursued in addition to investigating other purification methods.

3.5 Heterodifunctionalisation of benzoquinone

3.5.1 Heterodifunctionalisation – initial optimisation

Having successfully developed methodology for the homodifunctionalisation of benzoquinone, a natural progression of this work was the investigation of the heterodifunctionalisation of benzoquinone whereby 2 different R groups would be introduced onto the benzoquinone moiety. Given the lack of literature examples of a controlled and selective procedure, any advancement in this area would be of great interest and utility.

Initially, we looked to develop a heterodifunctionalisation reaction using a two-step process by using a monofunctionalised product as our substrate and then reacting it with a boronic acid bearing a different R group using conditions modified from our homodifunctionalisation procedure, to form the desired product (Scheme 84). Optimisation of this reaction was carried out by J. Jordan-Hore.



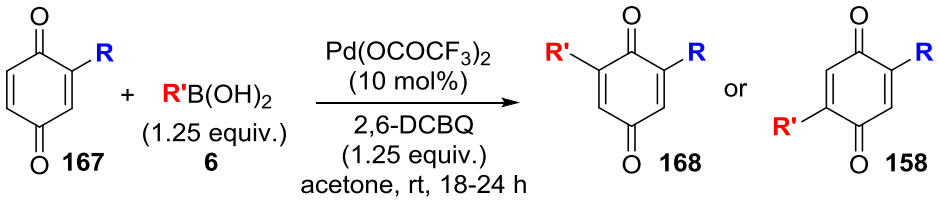
Scheme 84: Heterodifunctionalisation of benzoquinone – optimised reaction conditions

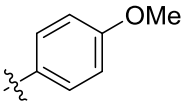
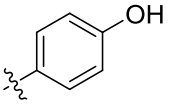
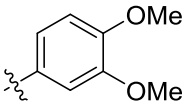
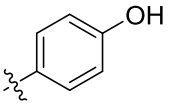
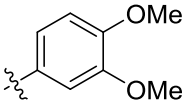
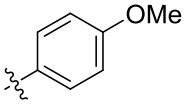
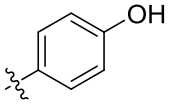
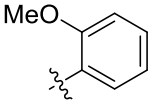
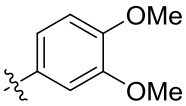
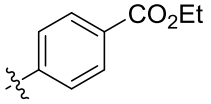
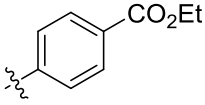
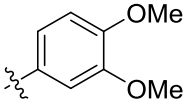
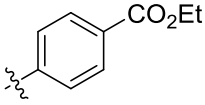
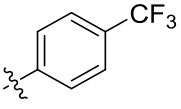
Using very similar conditions to the homodifunctionalisation procedure and reducing the equivalents of boronic acid and DCBQ used, heterodifunctionalised benzoquinones **168** and **158** could be synthesised in good yields at room temperature and with a reaction time of 18-24 h.

3.5.2 Boronic acid screen

Using the optimised reaction conditions, a boronic acid screen was carried out to probe the versatility of the reaction with a range of boronic acids (Table 20). Trends in the selectivity of the reaction (whether the 2,5 or 2,6 difunctionalised product is formed preferentially) are similar to those observed in the homodifunctionalisation investigations. The 2,5 isomer **158** is formed preferentially where the benzoquinone is

functionalised with electron-withdrawing groups and the selectivity switches to the 2,6 isomer **168** when electron-donating groups are present.



Entry	R	R'	Yield 168 (%)[a]	Yield 158 (%)[a]
1	**167c** 	**6d** 	**168cd** 73	**158cd** <5
2	**167o** 	**6d** 	**168od** 71	**158od** 10
3	**167o** 	**6c** 	**168oc** 65	**158oc** 21
4	**167d** 	**6d'** 	**168dd'** 50	**158dd'** 41
5	**167o** 	**6r** 	**168or** 44	**158or** 26
6	**167r** 	**6o** 	**168ro** 48	**158ro** 16
7[b]	**167r** 	**6b** 	**168rb** <5	**158rb** 47

[a]Isolated yields. [b]Products only moderately stable.

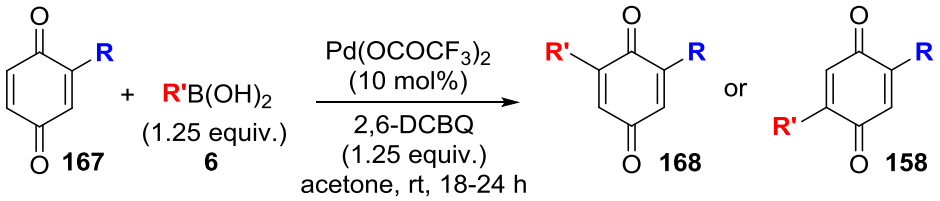
Table 20: Heterodifunctionalisation of benzoquinone – aryl boronic acid screen

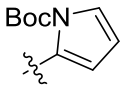
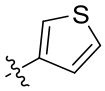
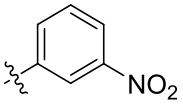
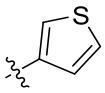
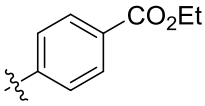
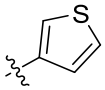
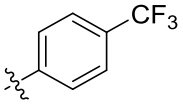
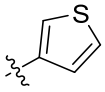
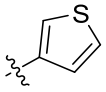
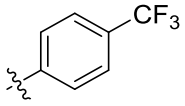
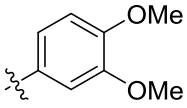
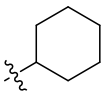
Yields were excellent where a monofunctionalised benzoquinone **167** with an electron-rich substituent was further functionalised with another electron-rich functional group to form the desired disubstituted product (Entries 1 to 4). Following the trend observed with homodifunctionalisation, preference for the 2,6 substituted product **168** is observed but the selectivity does drop when *ortho* substituted aryl boronic acids are used, yet the

yield remains very good (Entry 4). Understandably, a reduction in yield was observed and also a change in selectivity to predominantly the 2,5 disubstituted product **158** when both groups are electron-withdrawing (Entry 7).

We were intrigued to ascertain how the reaction outcome would be affected in terms of selectivity when the 2 substituents had different electronic properties. Starting with an electron-rich substituent and functionalising with an electron-poor substituent gave primarily the 2,6-difunctionalised product (Entry 5) albeit with significant amounts of 2,5 isomer formed. Synthesising the same product yet starting with an electron-poor monofunctionalised benzoquinone and functionalising with an electron-rich group gave the same selectivity (Entry 6) prompting us to conclude that the electronics of both the monofunctionalised starting material in addition to the electronics of the second group affect the selectivity of the reaction.

We also investigated whether our methodology could be applied to heterocyclic and cycloalkyl boronic acids despite the challenges experienced in the homodifunctionalisation reactions (Table 21).



Entry	R	R'	Yield 168 (%)[a]	Yield 158 (%)[a]
1[b]	**167w** 	**6u** 	trace	**158wu** 74
2[b,c,d]	**167i** 	**6u** 	trace	**158iu** 42
3[d]	**167r** 	**6u** 	trace	**158ru** 34
4[b,c,d]	**167b** 	**6u** 	**168bu** <28[e]	**158bu** 36
5[d]	**167u** 	**6b** 	**168ub** 23	**158ub** 31
6	**167o** 	**6x** 	-	-

[a]Isolated yields. [b]2.5 Equiv. boronic acid **6** used. [c]Treated with $FeCl_3$ at the end of reaction. [d]Products only moderately stable. [e]Impurities present.

Table 21: Heterodifunctionalisation of benzoquinone – heterocyclic and cycloalkyl boronic acid screen

After initial investigatory work with various heterocyclic boronic acids, we found that 3-thienyl boronic acid **6u** gave the most promising results. We investigated using 3-thienyl benzoquinone **167u** as our starting material and functionalising with various boronic acids, but found that higher yields were obtained by starting with various monofunctionalised benzoquinones and then functionalising with 3-thienyl boronic acid **6u** to form our desired products (see Entries 4 and 5 for one specific example). Additionally, for Entry 2, when the heterodifunctionalisation reaction was carried out by starting with 3-thienyl benzoquinone **167u** and functionalising with *m*-NO_2-C_6H_4-boronic acid, it was impossible to isolate both isomers due to coelution of the boronic

acid dimer with one of the isomers upon purification which therefore dictated the order of functionalisation.

Pleasingly reactions with heterocycles also showed selectivity, forming the 2,5 isomer preferentially (Entries 2-5). Additionally we found that a heterodifunctionalised product could be formed with 2 heterocylic groups (3-thienyl and *N*-Boc-2-pyrrole) in good yield and excellent 2,5 selectivity (Entry 1).

The reduction in yields observed for the heterodifunctionalisation reactions with electron-withdrawing and 3-thiophene boronic acids is most likely caused by the same factors which hampered yields in the homodifunctionalisation work (*vide supra*). Throughout our investigations, products bearing electron-withdrawing or heterocyclic groups were found to be unstable and challenging to isolate. Additionally, it is thought that the products compete with 2,6-DCBQ as oxidants in some circumstances and therefore these reasons are likely to be contributing factors to the reduced yields observed. Following on from our experience in overcoming these problems during our work on homodifunctionalisation, a couple of methods were employed to solve these issues and increase yields. Adding additional portions of boronic acid, or using $FeCl_3$ as an additional oxidant at the end of the reaction (Entries 1, 2 and 4) were found to increase yields although they still remain low compared to yields obtained with electron-donating boronic acids.

Next, we turned our attention to forming a heterodisubstituted product with an electron-rich aryl group and a cycloalkyl substituent (Entry 6). Using a prefunctionalised benzoquinone with an electron-rich aryl group **167o**, we carried out the reaction with cyclohexyl boronic acid **6x** and unfortunately a complex mixture of products was formed from which our desired product could not be isolated. This is certainly an area which could be investigated further in order to increase the scope of the reaction.

Additional heterodifunctionalised products which unfortunately could not be isolated include those shown below (Figure 5). Again, purification and stability posed problems for these reactions.

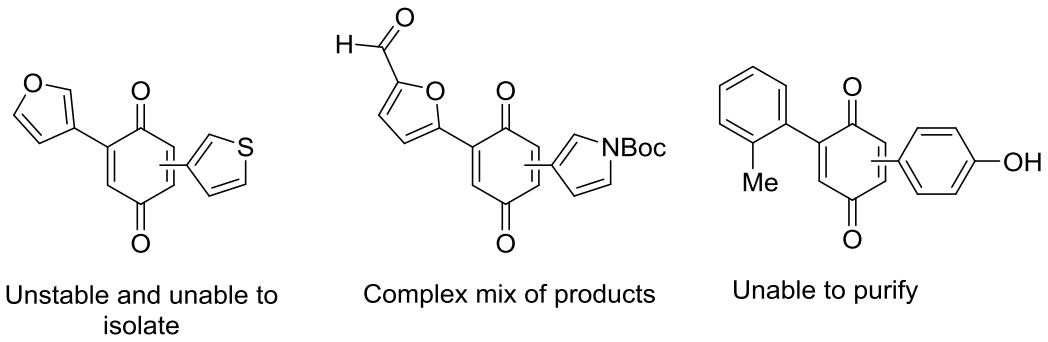
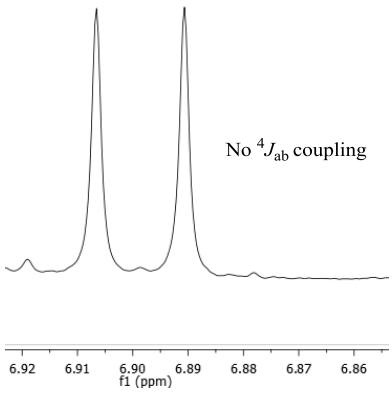


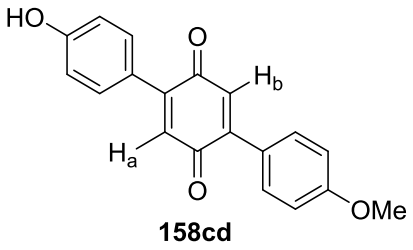
Figure 5: Heterodifunctionalised products which we were unable to isolate/synthesise using our methodology

Despite the aforementioned challenges in our investigations into the heterodifunctionalisation of benzoquinone, we have demonstrated that Pd(II) can be used to functionalise benzoquinone in a selective manner and excellent yields. Further work would be beneficial in this area to address in more detail the issues experienced with electron-withdrawing, heterocyclic and cycloalkyl boronic acids, in order to widen the scope of this reaction.

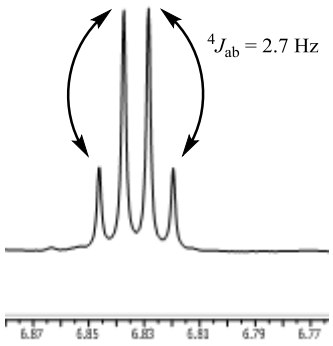
3.5.3 Characterisation of heterodifunctionalised products

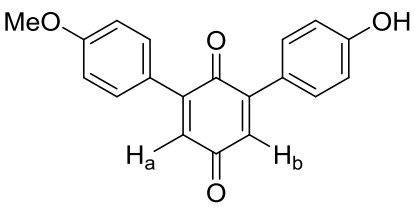
Whilst the 2,5 and 2,6 homodifunctionalised products could be differentiated by ^{13}C NMR analysis, this was not possible with heterodifunctionalised products and therefore distinguishing between 2,5 and 2,6 isomers was more challenging. In some cases two doublets could be observed in the ^{1}H NMR spectrum of the 2,6 isomer corresponding to the alkenyl protons coupling to one another (^{4}J coupling) (Figure 6). This coupling was absent from spectra for the 2,5 isomer, giving rise to two singlets for these protons.





158cd



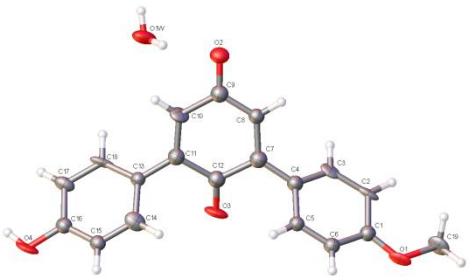


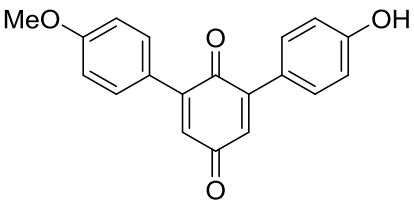
168cd

$^{4}J_{ab}$ = 2.7 Hz

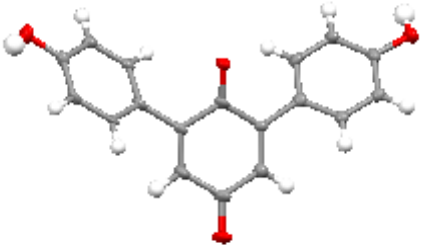
Figure 6: Comparison of ^{1}H NMR spectra for 2,5 and 2,6 heterodifunctionalised products

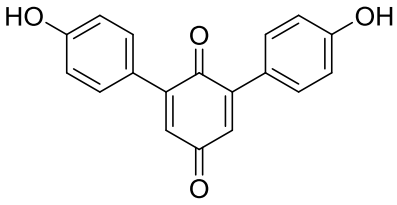
A crystal structure was also obtained for **168cd** in order to confirm our hypothesis (see Figure 7 below). Crystal structures were acquired for compounds **168dd** and **158bb**, as an additional characterisation method in order to confirm their identity.



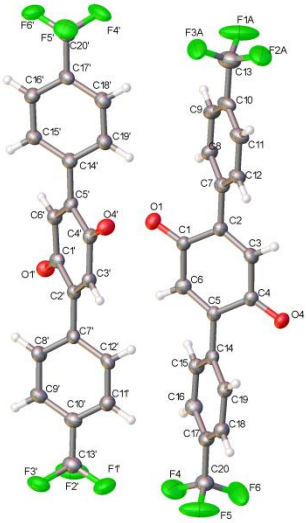


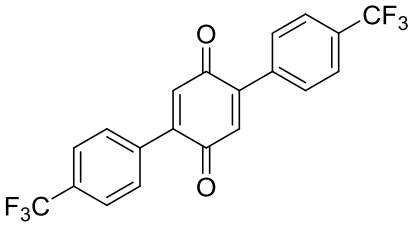
168cd





168dd

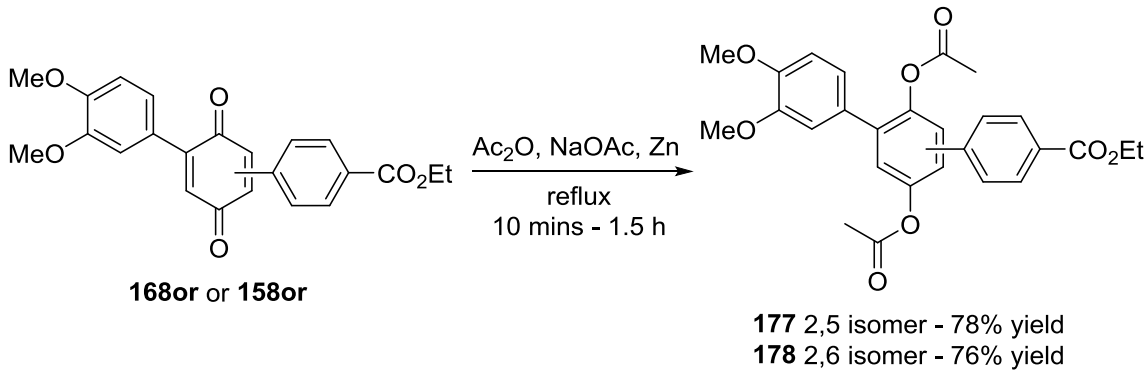




158bb

Figure 7: Crystal structures of homo- and hetero-difunctionalised products

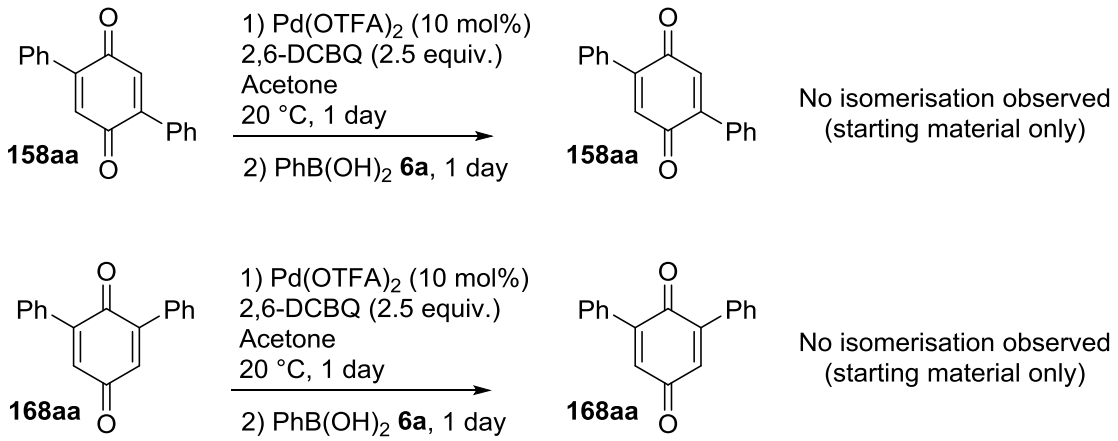
However, for products **168or** and **158or**, no ^{4}J coupling was evident in the ^{1}H NMR spectra and efforts to crystallise a sample to be able to ascertain the structure by X-ray crystallography were unsuccessful. Instead, by acetylating each isomer separately (using a method from literature for the diacetylation of 2,5- and 2,6-diaryl-1,4-hydroquinones),[32] we envisaged being able to differentiate between the isomers by NOESY (Scheme 85). However, after acetylation, ^{4}J coupling was in fact visible in the ^{1}H NMR spectrum of one of the products, and not the other, enabling us to confirm the identity of the 2,6 isomer without employing NOESY for characterisation.



Scheme 85: Acetylation of heterodifunctionalised products in order to confirm the structure by NOESY

3.6 Selectivity in the difunctionalisation reactions

During the course of our investigations, we were intrigued to observe the trends in selectivity in the homodifunctionalisation and heterodifunctionalisation reactions. In order to confirm that isomerisation was not occurring during the functionalisation reactions, two control experiments were carried out. Separate samples of the 2,5 and 2,6 isomers of bis-phenyl-1,4-benzoquinone (**158aa** and **168aa**) were subjected to the homodifunctionalisation reaction conditions (Scheme 86), followed by an additional portion of boronic acid after 24 h and the reactions monitored to see if formation of the other isomer was evident. Both reactions did not show any change from starting material to the other isomer, or other side products, thus confirming that isomerisation was not occurring during the difunctionalisation reactions.



Scheme 86: Control experiment to confirm isomerisation was not occurring during difunctionalisation reactions

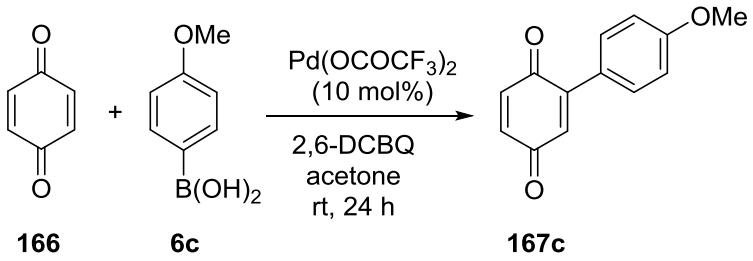
Given that some of the difunctionalisation reactions were also carried out at elevated temperature, it was important to investigate if temperature affects the ratio of products obtained. The homodifunctionalisation reaction with phenyl boronic acid **6a** was chosen as the test reaction and conducted at an elevated temperature of 40 °C. The ratio of 2,5 to 2,6 difunctionalised products was 1:1 and thus implies that temperature does not affect the ratio of isomers formed in these reactions.[*]

[*]In order to investigate further the selectivity observed in the difunctionalisation reactions, DFT calculations were carried out by the Macgregor group at Heriot-Watt University. This work is discussed in Section 3.8.

3.7 One pot heterodifunctionalisation reaction

During the course of our investigations into the heterodifunctionalisation of benzoquinone, we decided that it would be worth investigating the feasibility of a one-pot heterodifunctionalisation procedure. By forming a monofunctionalised product *in situ* and then further functionalising with a different aryl group, we would be able to showcase a simple yet effective method to form a difunctionalised product which to date could only be formed in a minimum of 2 steps from our work, and significantly more using current known literature methods.[37]

However, it was immediately evident that we would not be able to apply our standard conditions for monofunctionalisation to this procedure given that using 3 equivalents of benzoquinone would leave excess substrate in the reaction mixture during the second step. We therefore needed to reoptimise reaction conditions using an alternative oxidant to form the monofunctionalised product *in situ*. We used 2,6-dichloro-1,4-benzoquinone as an alternative oxidant in our optimisation studies as this had been effective in the homo- and hetero-difunctionalisation work. Various combinations of benzoquinone and 2,6-dichloro-1,4-benzoquinone were used and the product was isolated to give an indication of how much monofunctionalised product would be formed *in situ* during the one pot procedure (Table 22).



166 6c 167c

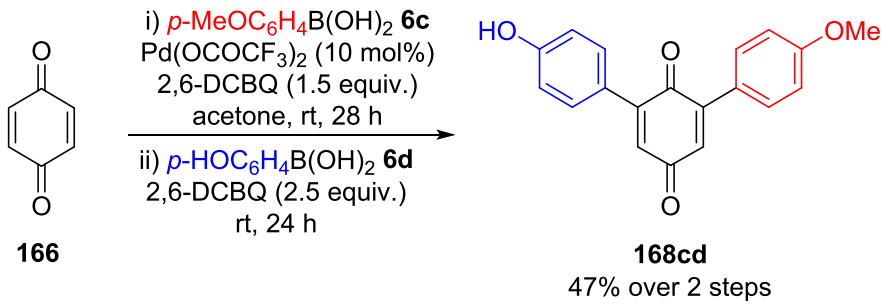
Entry	BQ (Equiv.)	2,6-DCBQ (Equiv.)	Yield 167c (%)[a]
1	3	0	80
2	2	0	40[b]
3	1	1	54[b]
4	1.5	1.5	71

[a]Isolated yields. [b]Diarylated product also present in crude mixture.

Table 22: Reducing the equivalents of benzoquinone

An additional challenge was to ideally avoid the formation of the homodifunctionalised benzoquinone. Using 3 equivalents of benzoquinone in the monofunctionalisation work avoided the formation of this by-product but as mentioned previously, in this case, this was not a viable solution. Fortunately whilst formation of the homodifunctionalisation product was evident when the equivalents of benzoquinone were reduced to 2 or 1 (Table 22, Entries 2 and 3), our studies showed that by reducing the equivalents of benzoquinone to 1.5 and using 1.5 equivalents of sacrificial oxidant, we were able to form the monofunctionalised product exclusively and in good yield (Table 22, Entry 4).

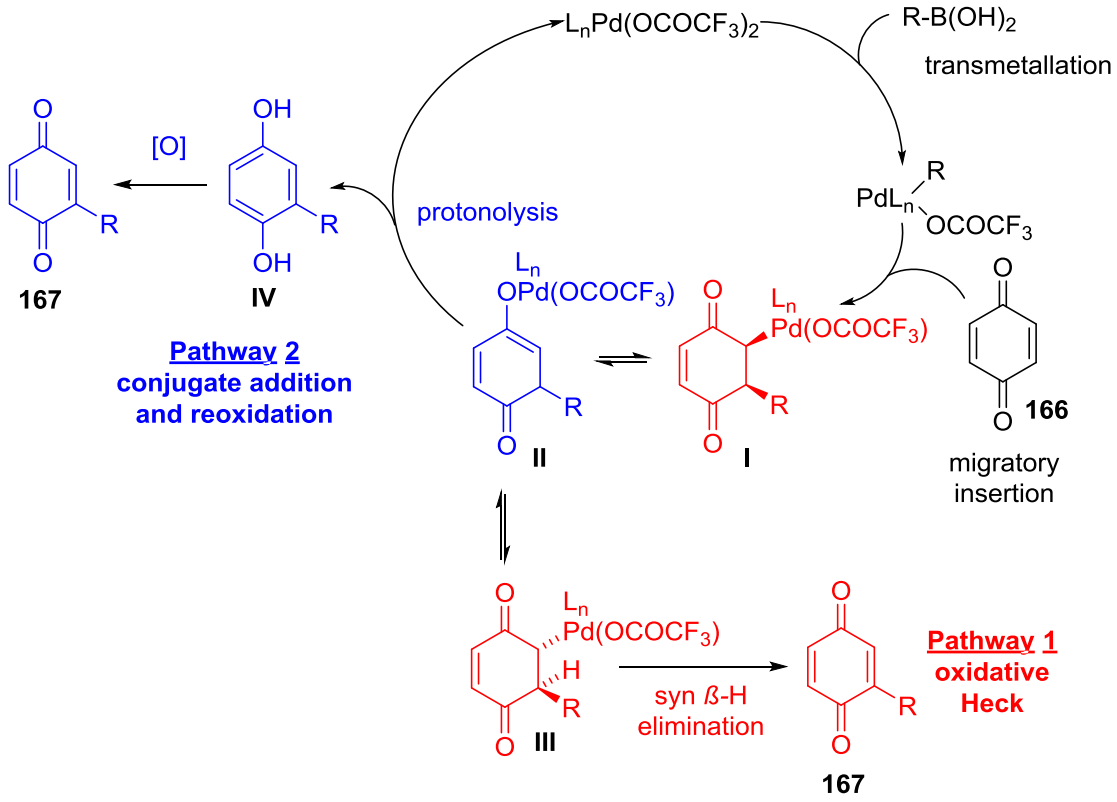
Using these optimised reaction conditions, we examined the second step of the reaction. Pleasingly, using excess (2.5 equivalents) of both DCBQ and the second boronic acid (4-hydroxyphenyl boronic acid **6d**), we obtained the desired product **168cd** in 47% yield, equating to a good average of 69% for each step of the reaction (Scheme 87).



Scheme 87: One pot C-H hetero-difunctionalisation of benzoquinone

3.8 Mechanism

Following our work detailed in chapter 2 where we demonstrated that the outcome of the Pd(II) catalysed reaction of cyclic enones and boronic acids can be switched between conjugate addition and oxidative Heck products, we propose 2 plausible mechanistic pathways for the functionalisation of benzoquinone (Scheme 88).



Scheme 88: Proposed mechanistic pathways for the functionalisation of benzoquinone

Both mechanistic pathways begin with the same steps; transmetallation of the boronic acid onto the active metal species followed by migratory insertion of benzoquinone **166** to give **I**. This species would then undergo enolate formation to form **II**, from which two possible mechanistic pathways can be followed in order to form the product **167**. Pathway 1 (marked in red) follows a direct Pd(II)-catalysed oxidative Heck mechanism or pathway 2 (marked in blue) forms the product *via* conjugate addition and reoxidation.

As previously discussed in chapter 2, in order for the reaction to proceed *via* an oxidative Heck pathway, formation of enolate **II** is vital to facilitate the final step in this cycle, *syn* β-hydride elimination, which cannot occur directly from species **I** due to it being conformationally restricted. Once *syn* β-hydride elimination has occurred, the

resulting Pd(0) species is then reoxidised to Pd(II) using either benzoquinone (for monofunctionalisation) or 2,6-DCBQ (for difunctionalisation) to regenerate the catalyst. Alternatively, species **II** can follow a conjugate addition pathway whereby protonolysis occurs, regenerating the catalyst, and the resulting hydroquinone species **IV** is then oxidised to form the desired functionalised benzoquinone.

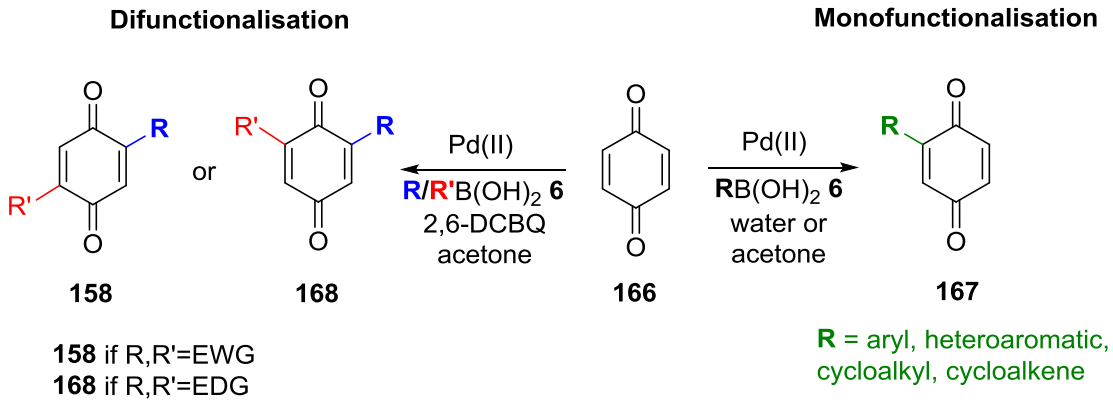
Both pathways are plausible and unfortunately we are unable to draw conclusions as to which is more likely from our experimental work. From the catalytic cycle, it is obvious that the two pathways differ in formation of the hydroquinone species, and so perhaps formation of this would be an indication of a conjugate addition route. However, formation of these species could occur through both pathways and not just the conjugate addition route as they could also be formed from their benzoquinone analogues acting as a competing oxidant in the oxidative Heck pathway, and thus appear as a side product (which has been observed in some difunctionalisation reactions – see section 3.4.2).

Additionally, we decided it would be worth investigating in more depth the selectivity observed in the difunctionalisation reactions. However, initial investigations (DFT calculations carried out by the Macgregor group at Heriot-Watt University) into the reasons for the selectivity observed have unfortunately been unable to shed light on plausible explanations for the trends observed. Similar charge distribution and LUMO coefficients were found for formation of both the 2,5 and 2,6 homodifunctionalised products bearing electron-donating or electron-withdrawing groups, from the corresponding monofunctionalised benzoquinones. However, subtle differences were observed in the energy involved in the migratory insertion step when electron-donating or electron-withdrawing groups are involved.

Further investigations into the mechanistic pathway would certainly be advantageous in order to shed light on which mechanistic pathway is more favourable, in addition to reasons for the selectivity observed.

3.9 Conclusions

This project has successfully developed the first palladium-catalysed direct functionalisation of benzoquinone. We have developed methodology to selectively carry out both mono and difunctionalisations in excellent yields. Our reaction conditions tolerate a wide variety of functional groups and complement current known methods for functionalising benzoquinone (Scheme 89).



Scheme 89: Pd(II)-catalysed direct functionalisation of benzoquinone

During the course of our studies we have found that regioselectivity of the difunctionalisation reactions is dependent on the electronic properties of the boronic acid used whereby electron-deficient and heterocyclic boronic acids preferentially form the 2,5 isomer and electron-donating boronic acids give rise to the 2,6 product. Additionally, our work has included developing a one-pot procedure for the heterodifunctionalisation of benzoquinone, resulting in a good yield of the desired heterodifunctionalised products.

3.10 Future work

Given that initial investigations have unfortunately been unable to shed light on the selectivity observed in the difunctionalisation reactions, further studies would enable us to gain more insight into the factors which influence selectivity. Additionally, investigations could be carried out in order to establish whether the functionalisation reactions proceed through a conjugate addition and reoxidation mechanism, or an oxidative Heck pathway (Scheme 88).

Due to the prevalence of the quinone moiety in natural products with biological applications, for instance betulinan A **143**,[6] omphalone **179**[52] or leucomelone **145**[7] (Figure 8), it would be useful to expand this work to other substrates such as substituted benzoquinones in order to investigate potential facile routes to such compounds. Exploratory investigations have indicated that with some further optimisation, this is certainly an area in which this project could be developed.

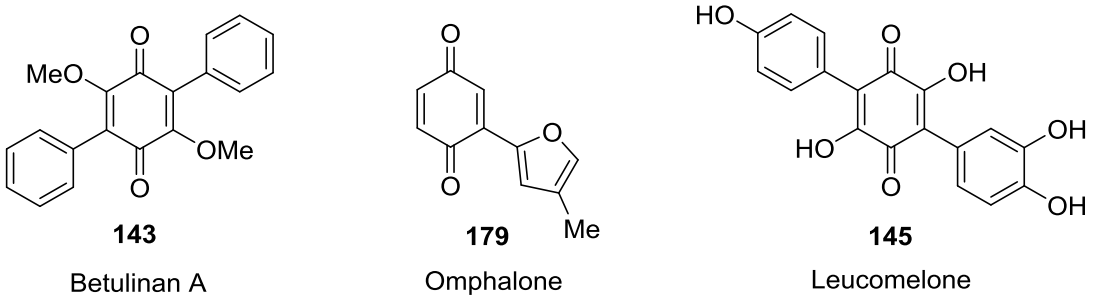
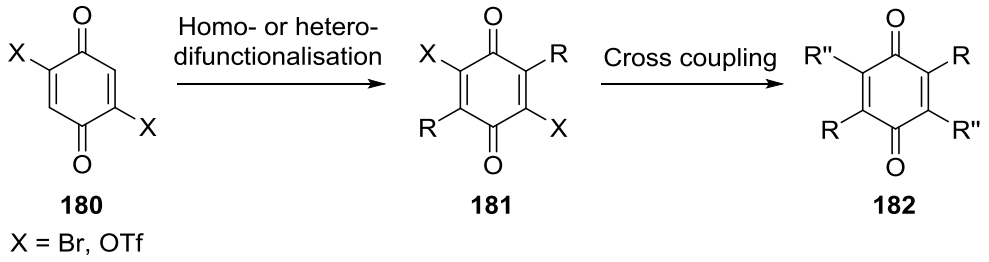


Figure 8: Biologically active quinone-based compounds

Additionally, our methodology could potentially be developed to form tetrasubstituted benzoquinones bearing four aryl/heteroaryl groups (Scheme 90). Such compounds have uses as ligands,[11-15] in molecular electronics[16] and also biological applications.[1-6] However, given current syntheses are lengthy, our methodology may provide a facile means of accessing such compounds.



Scheme 90: Potential application of difunctionalisation methodology to form tetrasubstituted products

3.11 Experimental section

General Experimental Considerations

^{1}H NMR spectra were recorded on Bruker AV 300, DPX 400 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26 ppm, δ_C at 77.00 ppm, $(CD_3)_2CO$ at δ_H 2.05 ppm, δ_C at 29.84 ppm or $(CD_3)_2SO$ at δ_H 2.50 ppm, δ_C at 39.52 ppm). *J* values are given in Hz and s, d, dd, t, q, hept., m and app. abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, heptet, multiplet, apparent and combinations thereof. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory or Thermo Scientific Nicolet iS5 FT-IR spectrometer, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Where necessary, sublimation of benzoquinone was carried out using a Kugelrohr distillation apparatus (Büchi B-585 or Büchi GKR-50).

Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and thin layer chromatography was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$, aqueous acidic ceric ammonium molybdate, acidic dinitrophenyl hydrazine or molecular iodine as appropriate. Petroleum ether refers to petroleum ether (40–60%) and EtOAc refers to ethyl acetate. Acetone was purchased from Fisher Scientific, all boronic acids were purchased from either Sigma Aldrich, Alfa Aesar or Fluorochem, palladium acetate trimer was provided by Johnson-Matthey and all other chemicals were provided by Sigma Aldrich. All chemicals were used without further purification unless otherwise stated. The reaction was performed without the need for dry solvents or inert atmosphere and all reactions were carried out in air.

Preparation of Palladium Trifluoroacetate[53]:

$Pd(OTFA)_2$ was prepared using the method specified in *Acta Cryst.* **1989**, *C45*, 1289 with minor modifications.

To a 100 mL round bottomed flask was added $Pd(OAc)_2$ (1.00 g, 4.45 mmol) and trifluoroacetic acid (25 mL). The resultant slurry was stirred for 10 min at 35 ^oC and the slurry was concentrated to dryness under reduced pressure. Trace TFA was removed *in vacuo*, to give $Pd(OTFA)_2$ as a brown dust (1.47 g, 99 %).

Purification of Benzoquinone:

Commercially available benzoquinone often appears either as an off yellow or green colour. This colouration is due to the presence of impurities, the most common being hydroquinone. Benzoquinone was purified prior to use by either simple flash column chromatography or recrystallisation from isopropyl alcohol. After purification benzoquinone was stored at room temperature without the exclusion of air. Pure benzoquinone should appear as a bright yellow, light and flocculent solid.

General procedures for the palladium(II)-catalysed C-H functionalisation of benzoquinone

General procedure 1 - Palladium(II)-catalysed C-H monofunctionalisation of benzoquinone in acetone:

Benzoquinone (3 equiv., 3 mmol), the boronic acid (1 equiv., 1 mmol) and palladium trifluoroacetate (7.5 mol%) were added to a round-bottomed flask equipped with a magnetic stir bar, acetone (12 mL) was then added and the reaction was stirred at room temperature for 18-24 h. Upon completion, as determined by thin layer chromatography, the mixture was evaporated to dryness, toluene (5 mL) and enough acetone to dissolve the heterogeneous mixture (0.5–1 mL) was added. The slurry was then purified directly by flash column chromatography to afford the monofunctionalised product. Where benzoquinone coeluted with the monofunctionalised product, it was removed by sublimation using a Kugelrohr distillation apparatus.

General procedure 2 - Palladium(II)-catalysed C-H monofunctionalisation of benzoquinone in water:

Benzoquinone (3 equiv., 3 mmol), the boronic acid (1 equiv., 1 mmol) and palladium trifluoroacetate (7.5 mol%) were added to a round-bottomed flask equipped with a magnetic stir bar, distilled water (12 mL) was then added, the solution briefly sonicated

to disperse the reagents where necessary and the reaction was stirred at room temperature for 18-24 h. Upon completion, as determined by thin layer chromatography, EtOAc (20 mL) and water (10 mL) were added. The layers were separated and the aqueous layer was washed with a EtOAc (3 × 20 mL). The organic layer was then washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. To the resultant solid, toluene (5 mL) and enough acetone to dissolve the heterogeneous mixture (0.5–1 mL) was added. The slurry was then purified directly by flash column chromatography to afford the monofunctionalised product. Where benzoquinone coeluted with the monofunctionalised product, it was removed by sublimation using a Kugelrohr distillation apparatus.

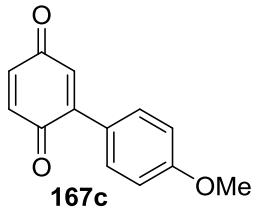
General procedure 3 - Palladium(II)-catalysed homo-difunctionalisation of benzoquinone:

Benzoquinone (1 equiv., 0.1 mmol), the boronic acid (2.5 equiv., 0.25 mmol), 2,6-dichlorobenzoquinone (2.5 equiv., 0.25 mmol) and palladium trifluoroacetate (10 mol%) were added to a round bottomed flask equipped with a magnetic stir bar. Acetone (0.340 mL) was then added and the reaction was stirred at room temperature for 48 h. Upon completion, as determined by thin layer chromatography, the mixture was evaporated to dryness, toluene (5 mL) and enough acetone to dissolve the heterogeneous mixture (0.5–1 mL) was added. The slurry was then purified directly by flash column chromatography to afford the difunctionalised product.

General procedure 4 - Palladium(II)-catalysed hetero-difunctionalisation of monofunctionalised benzoquinone derivatives:

The monofunctionalised benzoquinone derivative (1 equiv., 0.05 mmol), the boronic acid (1.25 equiv., 0.0625 mmol), 2,6-dichloro-1,4-benzoquinone (1.25 equiv., 0.0625 mmol) and palladium trifluoroacetate (10 mol%) were added to a round bottomed flask equipped with a magnetic stir bar. Acetone (0.170 mL) was then added and the reaction was stirred at 20 °C for 18 h. Upon completion, as determined by thin layer chromatography, the mixture was evaporated to dryness, toluene (5 mL) and enough acetone to dissolve the heterogeneous mixture (0.5–1 mL) was added. The slurry was then purified directly by flash column chromatography to afford the hetero-difunctionalised product.

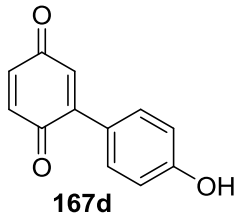
2-(4-Methoxyphenyl)-1,4-benzoquinone (167c)[38]



167c

General procedure 2 was followed to give the product **167c** in 88% yield as a brown solid; M. p. 108-110 °C; R_f 0.68 (3:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.8 Hz, 2H, Ar-H), 6.90 (d, J = 8.8 Hz, 2H, Ar-H), 6.82 – 6.69 (m, 3H, 3 × O=C-C<u>H</u>), 3.79 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.7 (C), 187.1 (C), 161.4 (C), 145.2 (C), 137.0 (CH), 136.3 (CH), 131.1 (CH), 130.9 (CH), 125.0 (C), 114.1 (CH), 55.4 (CH_3); HRMS (APCI) calculated for $[M+H]^+$ 215.0703, $C_{13}H_{11}O_3$ found: 215.0709.

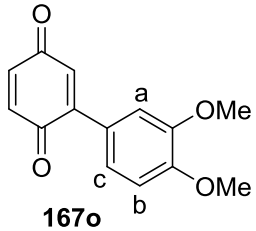
2-(4-Hydroxyphenyl)-1,4-benzoquinone (167d)[36]



167d

General procedure 1 was followed, using 6 equiv. benzoquinone to give the product **167d** in 64% yield as a bright red solid; M. p. 173-176 °C; R_f 0.56 (2:1 petroleum ether:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.84 (s, 1H, O<u>H</u>), 7.48 (d, J = 8.7 Hz, 2H, Ar-H), 6.92 (d, J = 8.7 Hz, 2H, Ar-H), 6.87 – 6.79 (m, 3H, 3 × O=C-C<u>H</u>); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 188.3 (C), 187.9 (C), 160.2 (C), 146.0 (C), 138.0 (CH), 136.9 (CH), 132.0 (CH), 131.9 (CH), 125.2 (C), 116.2 (CH); ν_{max}/cm^{-1} 3317 br str, 1646 v str, 1607 str, 1514 m, 1434 w, 1343 w, 1252 m, 1098 w, 978 w, 900 v str, 840 v str; HRMS (APCI) calculated for $[M+H]^+$ 201.0546, $C_{12}H_9O_3$ found: 201.0546.

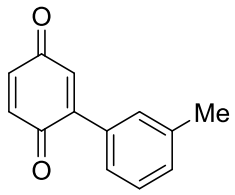
2-(3,4-Dimethoxyphenyl)-1,4-benzoquinone (167o)[38]



167o

General procedure 2 was followed on gram scale (10.5 mmol, 1.136 g benzoquinone) to give the product **167o** in 70% yield as a black solid; M. p. 137-140 °C; R_f 0.43 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (dd, J = 8.4, 2.1 Hz, 1H, H_c), 7.05 (d, J = 2.1 Hz, 1H, H_a), 6.94 (d, J = 8.4 Hz, 1H, H_b), 6.86 – 6.82 (m, 3H, 3 × O=C-C<u>H</u>), 3.93 (s, 3H, OC<u>H</u>$_3$), 3.92 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.6 (C), 187.0 (C), 151.1 (C), 148.9 (C), 145.2 (C), 137.1 (CH), 1362 (CH), 131.3 (CH), 125.2 (C), 122.7 (CH), 112.18 (CH), 111.1 (CH), 56.01 (CH_3), 55.99 (CH_3); ν_{max}/cm^{-1} 1652 v str, 1515 str, 1263 str, 1146 m, 1093 m, 1023 m, 901 w, 860 w.

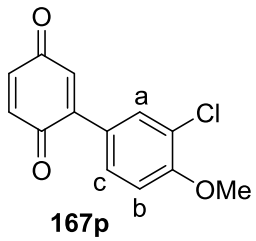
2-(3-Methylphenyl)-1,4-benzoquinone (167e)[38]



167e

General procedure 2 was followed to give the product **167e** in 90% yield as a brown solid; M. p. 84-87 °C; R_f 0.45 (10:1 petroleum ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 – 7.00 (m, 4H, Ar-H), 6.92 – 6.61 (m, 3H, 3 × O=C-C<u>H</u>), 2.34 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.6 (C), 186.7 (C), 146.2 (C), 138.2 (C), 137.1 (CH), 136.2 (CH), 132.62 (C), 132.56 (CH), 130.9 (CH), 129.8 (CH), 128.4 (CH), 126.4 (CH), 21.4 (CH_3); ν_{max}/cm^{-1} 2922 w, 2856 str, 1643 v str, 1602 m, 1590 str, 189 w, 1296 str, 1098 str, 900 str, 888 str, 781 v str, 697 v str; HRMS (APCI) calculated for $[M+H]^+$ 199.0754, $C_{13}H_{11}O_2$ found: 199.0753.

2-(3-Chloro-4-methoxyphenyl)-1,4-benzoquinone (167p)

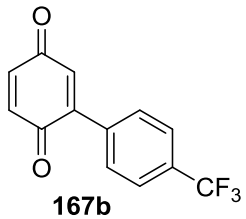


167p

General procedure 2 was followed to give the product **167p** in 48% yield as a red solid; M. p. 160-162 °C; R_f 0.20 (5:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 2.2 Hz, 1H, H_a), 7.43 (dd, J = 8.6, 2.2 Hz, 1H, H_c), 6.99 (d, J = 8.6 Hz, 1H, H_b), 6.88 – 6.78 (m, 3H, 3 × O=C-C<u>H</u>), 3.96 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.4 (C), 186.6 (C), 156.6 (C), 144.0 (C), 137.0 (CH), 136.3 (CH), 131.7 (CH), 131.0 (CH), 129.1 (CH), 125.7 (C), 122.9 (C), 111.8 (CH), 56.3 (CH_3); ν_{max}/cm^{-1} 3062 w, 2954 w, 1653 v str, 1599 str, 1588 str, 1505 str, 1303 str, 1266 str, 1064 str; HRMS (APCI) calculated for $[M+H]^+$ 249.0313, $C_{13}H_{10}O_3Cl$ found: 249.0312.

Note: General procedure 1 was carried out by J. Jordan-Hore to give product **167p** in 78% yield.

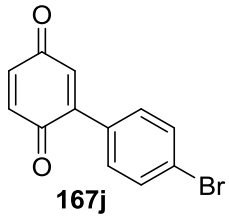
2-(4-Trifluoromethylphenyl)-1,4-benzoquinone (167b)[38]



167b

General procedure 2 was followed to give the product **167b** in 64% yield as a black solid; M. p. 109-113 °C; R_f 0.17 (5:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.1 Hz, 2H, Ar-H), 7.59 (d, J = 8.1 Hz, 2H, Ar-H), 6.93 – 6.85 (m, 3H, 3 × O=C-C<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.1 (C), 186.0 (C), 144.7 (C), 137.0 (CH), 136.4 (CH), 136.1 (C), 133.6 (CH), 131.9 (C, q, J = 32.8 Hz), 129.6 (CH), 125.5 (CH, q, J = 3.7 Hz), 123.8 (C, q, J = 272.4 Hz); ν_{max}/cm^{-1} 2930 w, 1649 v str, 1597 m , 1406 m, 1329 str, 1120 v str, 1107 v str, 1069 v str, 908 v str, 860 str, 848 str.

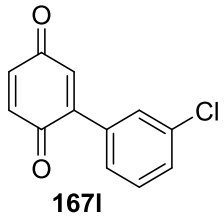
2-(4-Bromophenyl)-1,4-benzoquinone (167j)[37]



167j

General procedure 2 was followed to give the product **167j** in 82% yield as a bright yellow solid; M. p. 112-115 °C; R_f 0.38 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.5 Hz, 2H, Ar-H), 7.36 (d, J = 8.5 Hz, 2H, Ar-H), 6.92 – 6.79 (m, 3H, 3 × O=C-C<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.3 (C), 186.2 (C), 144.8 (C), 137.0 (CH), 136.4 (CH), 132.6 (CH), 131.8 (CH), 131.4 (C), 130.8 (CH), 124.9 (C); HRMS (APCI) calculated for $[M+H]^+$ 262.9702, $C_{12}H_8O_2Br$ found: 262.9700.

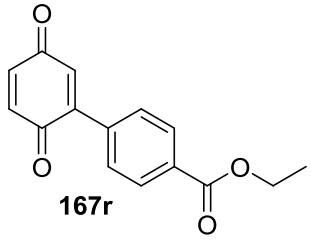
2-(3-Chlorophenyl)-1,4-benzoquinone (167l)[43]



167l

General procedure 2 was followed to give the product **167l** in 89% yield as a dark yellow solid; M. p. 142-144 °C; R_f 0.38 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 – 7.47 (m, 1H, Ar-H), 7.47 – 7.41 (m, 1H, Ar-H), 7.41 – 7.33 (m, 2H, Ar-H), 6.95 – 6.73 (m, 3H, 3 × O=C-C<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.2 (C), 186.1 (C), 144.6 (C), 137.0 (CH), 136.4 (CH), 134.5 (C), 134.3 (C), 133.1 (CH), 130.1 (CH), 129.8 (CH), 129.3 (CH), 127.4 (CH); ν_{max}/cm^{-1} 3077 w, 1654 v str, 1590 str, 1562 str, 1344 str, 1299 str, 1099 str, 1085 str, 903 v str, 883 v str, 833 v str, 690 v str; HRMS (APCI) calculated for $[M+H]^+$ 219.0207, $C_{12}H_8O_2Cl$ found: 219.0213.

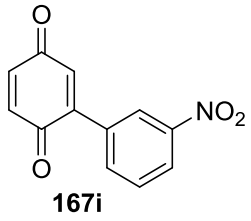
2-(4-Ethoxycarbonylphenyl)-1,4-benzoquinone (167r)



167r

General procedure 2 was followed to give the product **167r** in 75% yield as a dark green solid; M. p. 119-123 °C; R_f 0.57 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.7 Hz, 2H, Ar-H), 7.55 (d, J = 8.7 Hz, 2H, Ar-H), 6.94 – 6.85 (m, 3H, 3 × O=C-C<u>H</u>), 4.41 (q, J = 7.1 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.41 (t, J = 7.1 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.2 (C), 186.1 (C), 165.9 (C), 145.1 (C), 137.0 (CH), 136.8 (C), 136.4 (CH), 133.4 (CH), 131.8 (C), 129.6 (CH), 129.2 (CH), 61.3 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 2929 w, 1716 w, 1651 v str, 1596 str, 1407 str, 1326 v str, 1278 str, 1168 str, 1120 v str, 1068 v str, 908 v str, 732 v str; HRMS (APCI) calculated for $[M+H]^+$ 257.0808, $C_{15}H_{13}O_4$ found: 257.0811.

2-(3-Nitrophenyl)-1,4-benzoquinone (167i)[45]

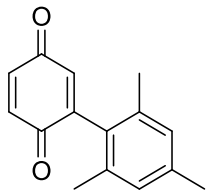


167i

General procedure 2 was followed, but the reaction required 48 h at 50 °C to give the product **167i** in 53% yield as a grey solid; M. p. 118-125 °C; R_f 0.14 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (t, J = 1.9 Hz, 1H, Ar-H), 8.36 – 8.30 (m, 1H, Ar-H), 7.85 – 7.79 (m, 1H, Ar-H), 7.69 – 7.62 (m, 1H, Ar-H), 6.98 – 6.90 (m, 3H, 3 × O=C-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.8 (C), 185.7 (C), 148.3 (C), 143.7 (C), 136.9 (CH), 136.6 (CH), 135.1 (CH), 134.1 (C), 133.8 (CH), 129.6 (CH), 124.7 (CH), 124.3 (CH); ν_{max}/cm^{-1} 3084 w, 2925 w, 1658 v str, 1614 str, 1592 str, 1528 v str, 1345 v str, 1295 str, 1275 str, 1094 v str, 902 v str, 733 v str; HRMS (APCI) calculated for $[M+H]^+$ 230.0448, $C_{12}H_8O_4N$ found: 230.0450.

Note: General procedure 1 was carried out by J. Jordan-Hore (requiring 48 h at 50 °C) to give product **167i** in 71% yield.

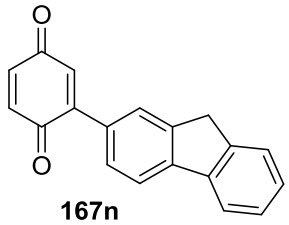
2-(2,4,6-Trimethylphenyl)-1,4-benzoquinone (167s)



167s

General procedure 2 was followed to give the product **167s** in 68% yield as a dark red thick oil; R_f 0.43 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (s, 2H, Ar-H), 6.90 – 6.64 (m, 3H, 3 × O=C-C<u>H</u>), 2.31 (s, 3H, C<u>H</u>$_3$), 2.08 (s, 6H, 2 × C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.4 (C), 186.2 (C), 148.1 (C), 138.4 (C), 136.7 (CH), 136.4 (CH), 135.4 (CH), 135.3 (C), 129.7 (C), 128.3 (CH), 21.0 (CH_3), 20.2 (CH_3); ν_{max}/cm^{-1} 2921 w, 1656 v str, 1611 w, 1597 w, 1282 str, 1090 m, 912 m, 835 m; HRMS (APCI) calculated for $[M+H]^+$ 227.1067, $C_{15}H_{15}O_2$ found: 227.1067.

2-(2-Fluorenyl)-1,4-benzoquinone (167n)



167n

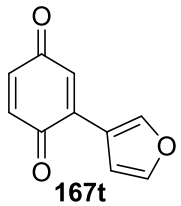
General procedure 2 was followed to give the product **167n** in 53% yield as a brown solid; M. p. 195-198 °C; R_f 0.59 (3:1 petroleum ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 – 7.77 (m, 2H, Ar-H), 7.74 – 7.65 (m, 1H, Ar-H), 7.63 – 7.46 (m, 2H, Ar-H), 7.46 – 7.31 (m, 2H, Ar-H), 6.98 – 6.80 (m, 3H, 3 × O=C-C<u>H</u>), 3.96 (s, 2H, C<u>H</u>$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.6 (C), 187.0 (C), 146.1 (C), 143.8 (C), 143.8 (C), 143.4 (C), 140.7 (C), 137.1 (CH), 136.3 (CH), 132.1 (CH), 130.9 (C), 128.2 (CH), 127.6 (CH), 127.0 (CH), 126.0 (CH), 125.2 (CH), 120.5 (CH), 119.9 (CH), 36.9 (CH_2); ν_{max}/cm^{-1} 3053 w, 2924 w, 1645 v str, 1589 str, 1456 w,

767 str, 732 v str; HRMS (APCI) calculated for $[M+H]^+$ 273.0910, $C_{19}H_{13}O_2$ found: 273.0907.

Note: General procedure 1 was carried out by J. Jordan-Hore to give product **167n** in 81% yield.

C-H Monofunctionalisation of benzoquinone with heterocyclic boronic acids: General procedures 1 and 2 used. Reactions carried out on a 0.5 mmol scale with a reaction time of 40-43 h.

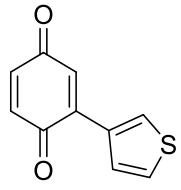
2-(3-Furanyl)-1,4-benzoquinone (167t)



167t

General procedure 1 was followed to give the product **167t** in 52% yield as a dark brown solid; M. p. decomposes at 110 °C; R_f 0.59 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (s, 1H, HetAr-H), 7.48 (dd, J = 2.0, 1.5 Hz, 1H, HetAr-H), 6.87 – 6.72 (m, 3H, 3 × O=C-C<u>H</u>), 6.67 – 6.61 (m, 1H, HetAr-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.4 (C), 186.4 (C), 146.1 (CH), 143.6 (CH), 138.0 (C), 137.1 (CH), 136.2 (CH), 128.5 (CH), 118.0 (C), 107.7 (CH); ν_{max}/cm^{-1} 2973 w, 1651 v str, 1597 str, 1296 str, 1164 m, 1033 str, 913 str, 806 str; HRMS (APCI) calculated for $[M+H]^+$ 175.0390, $C_{10}H_7O_3$ found: 175.0390.

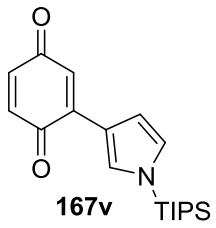
2-(3-Thienyl)-1,4-benzoquinone (167u)



167u

General procedure 1 was followed to give the product **167u** in 62% yield as a brown solid; M. p. 137-139 °C; R_f 0.50 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (dd, J = 2.6, 1.6 Hz, 1H, HetAr-H), 7.43 – 7.35 (m, 2H, HetAr-H), 6.96 – 6.76 (m, 3H, 3 × O=C-C<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.9 (C), 186.8 (C), 139.2 (C), 137.1 (CH), 136.1 (CH), 132.8 (C), 129.9 (CH), 129.8 (CH), 126.7 (CH), 126.2 (CH); ν_{max}/cm^{-1} 3054 w, 1659 v str, 1646 v str, 1578 v str, 1510 m, 1419 m, 1371 m, 1286 v str, 1096 v str, 907 v str, 789 v str; HRMS (APCI) calculated for $[M+H]^+$ 191.0161, $C_{10}H_7O_2S$ found: 191.0166.

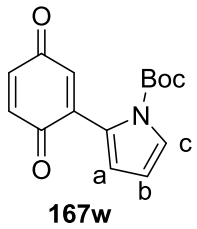
2-(1-(Triisopropylsilyl)-3-pyrrolyl)-1,4-benzoquinone (167v)



167v

General procedure 1 was followed to give the product **167v** in 41% yield as a dark red solid; M. p. 75-78 °C; R_f 0.60 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (dd, J = 2.0, 1.4 Hz, 1H, HetAr-H), 6.84 – 6.68 (m, 4H, 3 × O=C-C<u>H</u> and HetAr-H), 6.61 (dd, J = 3.0, 1.4 Hz, 1H, HetAr-H), 1.49 (hept., J = 7.5 Hz, 3H, C<u>H</u>$(CH_3)_2$), 1.12 (d, J = 7.5 Hz, 18H, Si(CH(C<u>H</u>$_3)_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.1 (C), 188.0 (C), 140.1 (C), 136.9 (CH), 136.2 (CH), 129.9 (CH), 125.7 (CH), 125.3 (CH), 118.3 (C), 109.3 (CH), 17.7 (CH_3), 11.6 (CH); ν_{max}/cm^{-1} 2950 str, 2866 str, 1663 v str, 1650 v str, 1573 v str, 1495 str, 1285 v str, 1221 v str, 1082 v str, 884 v str, 658 v str; HRMS (NSI) calculated for $[M+H]^+$ 330.1884, $C_{19}H_{28}O_2NSi$ found: 330.1886.

2-(1-(*tert*-Butoxycarbonyl)-2-pyrrolyl)-1,4-benzoquinone (167w)



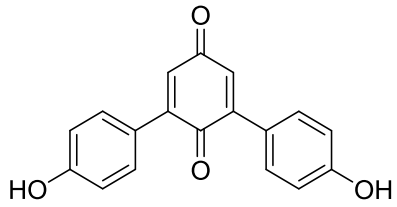
167w

General procedure 2 was followed to give the product **167w** in 75% yield as a dark red thick oil; R_f 0.66 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (dd, J = 3.4, 1.7 Hz, 1H, H_c), 6.86 – 6.70 (m, 3H, 3 × O=C-C<u>H</u>), 6.37 (dd, J = 3.4, 1.7 Hz, 1H, H_a), 6.25 (t, J = 3.4 Hz, 1H, H_b), 1.51 (s, 9H, O<u>^{t}Bu</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.5 (C), 185.8 (C), 148.6 (C), 141.7 (C), 136.7 (CH), 136.6 (CH), 130.1 (CH), 126.6 (C), 124.9 (CH), 117.0 (CH), 111.2 (CH), 84.7 (C), 27.8 (CH_3); ν_{max}/cm^{-1} 2981 w, 1744 v str, 1661 v str, 1595 w, 1468 w, 1404 w, 1314 v str, 1139 v str; HRMS (APCI) calculated for $[M+H]^+$ 274.1074, $C_{15}H_{16}O_4N$ found: 274.1070.

Palladium(II)-catalysed homo-difunctionalisation of benzoquinone

2,6-Bis-(4-hydroxyphenyl)-1,4-benzoquinone (168dd) and **2,5-Bis-(4-hydroxyphenyl)-1,4-benzoquinone (158dd)**

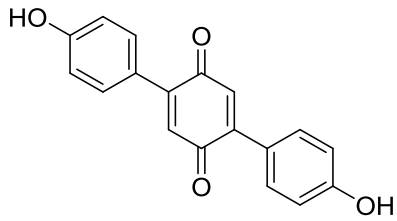
General procedure 3 was followed to yield **168dd** and **158dd** in an approximate >10:1 ratio.



Major product
168dd

Dark red solid, 71% yield; M. p. 211-215 °C; R_f 0.39 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.82 (s, 2H, OH), 7.52 (d, J = 8.8 Hz, 4H, Ar-H), 6.93 (d, J = 8.8 Hz, 4H, Ar-H), 6.82 (s, 2H, O=C-CH); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 188.01 (C), 187.8 (C), 160.1 (C), 147.1 (C), 132.1 (CH), 131.0 (CH), 125.9 (C), 116.1 (CH); ν_{max}/cm^{-1} 3318 br str, 1637 v str, 1605 v str, 1579 v str, 1506 v str, 1438 str, 1232 v str, 1176 v str, 1105 v str, 910 str, 840 v str, 730 str; HRMS (APCI) calculated for $[M+H]^+$ 293.0808, $C_{18}H_{13}O_4$ found: 293.0810.

A crystal structure was also obtained of this product. This can be found in section 3.5.3.

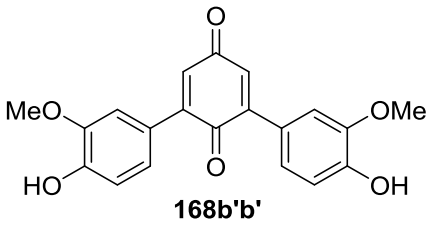


Minor product
158dd

Black solid, <5% yield; M. p. >300 °C; R_f 0.39 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.00 (s, 2H, OH), 7.47 (d, J = 8.8 Hz, 4H, Ar-H), 6.90 (s, 2H, O=C-CH), 6.84 (d, J = 8.8 Hz, 4H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 187.3 (C), 159.4 (C), 144.2 (C), 131.2 (CH), 130.7 (CH), 123.2 (C), 115.4 (CH); ν_{max}/cm^{-1} 3379 br, 2567 m, 2506 m, 1637 v str, 1594 v str, 1507 v str, 1347 m, 1250 v str, 1171 str, 992 m, 899 str, 805 str; HRMS (APCI) calculated for $[M-H]^-$ 291.0663, $C_{18}H_{11}O_4$ found: 291.0658.

2,6-Bis-(4-hydroxy-3-methoxyphenyl)-1,4-benzoquinone (168b'b')

General procedure 3 was followed to yield **168b'b'** as the major product. Evidence of a minor product, believed to be the 2,5 isomer, was observed. However, it was impossible to isolate pure for characterisation.

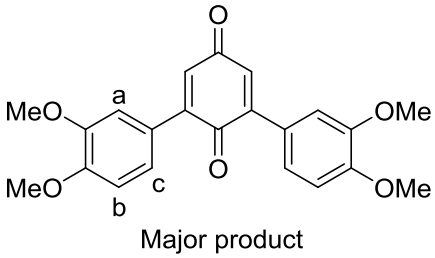


168b'b'

Dark red solid, 73% yield; M. p. 178-179 °C; R_f 0.66 (1:1.5 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 – 7.05 (m, 4H, Ar-H), 6.99 (d, J = 8.4 Hz, 2H, Ar-H), 6.86 (s, 2H, O=C-C<u>H</u>), 5.87 (s, 2H, OH), 3.94 (s, 6H, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.6 (C), 187.0 (C), 147.7 (C), 146.4 (C), 145.9 (C), 131.3 (CH), 125.3 (C), 123.3 (CH), 114.6 (CH), 111.9 (CH), 56.1 (CH_3); ν_{max}/cm^{-1} 3287 br, 2938 w, 1631 m, 1586 m, 1563 m, 1509 str, 1426 str, 1259 str, 899 str, 855 m; HRMS (APCI) calculated for $[M+H]^+$ 353.1020, $C_{20}H_{17}O_6$ found: 353.1016.

2,6-Bis-(3,4-dimethoxyphenyl)-1,4-benzoquinone (168oo)[54]

General procedure 3 was followed to yield **168oo** as the major product. Evidence of a minor product, believed to be the 2,5 isomer was observed. However, it was impossible to isolate pure for characterisation.

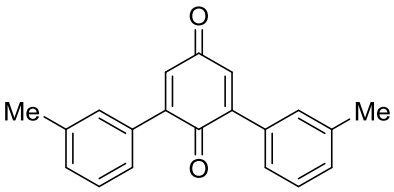


Major product
168oo

Dark red solid, 58% yield; M. p. 160-164 °C; R_f 0.47 (95:5 dichloromethane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (dd, J = 8.4, 2.1 Hz, 2H, H_c), 7.09 (d, J = 2.1 Hz, 2H, H_a), 6.95 (d, J = 8.4 Hz, 2H, H_b), 6.87 (s, 2H, O=C-C<u>H</u>), 3.93 (s, 6H, OC<u>H</u>$_3$); 3.92 (s, 6H, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.6 (C), 186.8 (C), 150.9 (C), 148.8 (C), 145.8 (C), 131.4 (CH), 125.8 (C), 122.8 (CH), 112.3 (CH), 111.0 (CH), 56.00 (CH_3), 55.97 (CH_3); ν_{max}/cm^{-1} 3018 w, 2936 w, 2838 w, 1640 v str, 1596 str, 1510 v str, 1463 w, 1255 v str, 1145 m, 1021 w, 746 v str; HRMS (APCI) calculated for $[M+H]^+$ 381.1333, $C_{22}H_{21}O_6$ found: 381.1334.

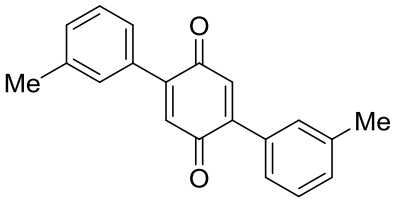
2,6-Bis-(3-methylphenyl)-1,4-benzoquinone (168ee)[55] and **2,5-Bis-(3-methylphenyl)-1,4-benzoquinone (158ee)**[55]

General procedure 3 was followed to yield **168ee** and **158ee** in an approximate 2:1 ratio.



Major product
168ee

Dark brown thick oil, 53% yield; R_f 0.83 (4:1 petroleum ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 – 7.14 (m, 8H, Ar-H), 6.83 (s, 2H, O=C-C<u>H</u>), 2.34 (s, 6H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.7 (C), 186.3 (C), 146.7 (C), 138.2 (C), 133.1 (C), 132.5 (CH), 130.8 (CH), 130.0 (CH), 128.4 (CH), 126.5 (CH), 21.4 (CH_3); ν_{max}/cm^{-1} 2923 w, 1647 v str, 1591 w, 1485 m, 1303 w, 771 w; HRMS (APCI) calculated for $[M+H]^+$ 289.1223, $C_{20}H_{17}O_2$ found: 289.1220.

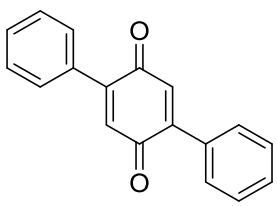


Minor product
158ee

Dark brown thick oil, 28% yield; R_f 0.90 (4:1 petroleum ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 – 7.27 (m, 8H, Ar-H), 6.95 (s, 2H, O=C-C<u>H</u>), 2.42 (s, 6H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.1 (C), 145.7 (C), 138.3 (C), 133.1 (CH), 132.5 (C), 130.9 (CH), 129.9 (CH), 128.4 (CH), 126.4 (CH), 21.5 (CH_3); ν_{max}/cm^{-1} 2923 w, 1646 v str, 1580 w, 1349 w, 785 str; HRMS (APCI) calculated for $[M+H]^+$ 289.1223, $C_{20}H_{17}O_2$ found: 289.1224.

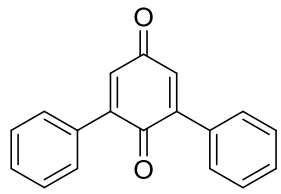
2,5-Diphenyl-1,4-benzoquinone (158aa)[56] and **2,6-Diphenyl-1,4-benzoquinone (168aa)**[56]

General procedure 3 was followed to yield **158aa** and **168aa** in an approximate 3:2 ratio.



Major product
158aa

Yellow solid, 44% yield; M. p. 214-218 °C; R_f 0.62 (80:20 dichloromethane:hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 – 7.51 (m, 4H, Ar-H), 7.51 – 7.43 (m, 6H, Ar-H), 6.97 (s, 2H, O=C-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.0 (C), 145.6 (C), 133.1 (CH), 132.5 (C), 130.1 (CH), 129.3 (CH), 128.6 (CH); ν_{max}/cm^{-1} 3053 w, 1640 v str, 1604 w, 1488 w, 1444 w, 904 v str, 769 v str, 696 v str.



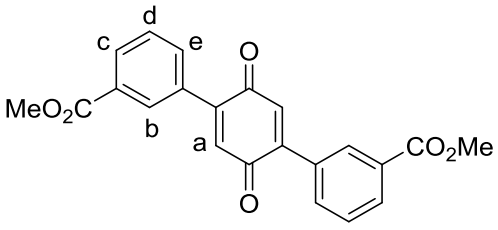
Minor product
168aa

Red solid, 29% yield; M. p. 126-132 °C; R_f 0.28 (80:20 dichloromethane:hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 – 7.49 (m, 4H, Ar-H), 7.49 – 7.43 (m, 6H, Ar-H), 6.93 (s, 2H, O=C-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.6 (C), 186.1 (C), 146.5 (C), 133.2 (C), 132.6 (CH), 130.0 (CH), 129.4 (CH), 128.5 (CH); ν_{max}/cm^{-1} 3037 w, 1644 v str, 1601 w, 1591 w, 1494 w, 1447 str, 743 v str, 687 v str.

2,5-Bis-(3-methoxycarbonylphenyl)-1,4-benzoquinone (158hh) and **2,6-Bis-(3-methoxycarbonylphenyl)-1,4-benzoquinone (168hh)**

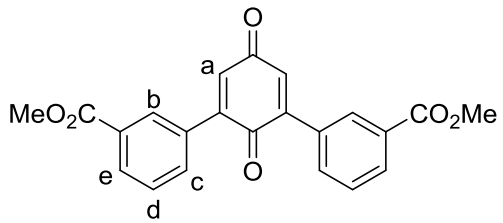
General procedure 3 was followed using an elevated temperature of 35 °C. Additional portions of catalyst (0.005 mmol, 5 mol%) and boronic acid (0.050 mmol, 0.5 equiv.) were added after 24 h followed by a portion of $FeCl_3$ (0.400 mmol, 4 equiv.) as an additional oxidant after 45 h. Following purification by column chromatography, an additional portion of $FeCl_3$ (0.400 mmol, 4 equiv.) was added to the column wash, stirred for 18 h and the residue purified to yield further product. As the 2,5 and 2,6 isomers were not fully separable, a mixture of **158hh** and **168hh** was isolated in 75% yield and a 41:59 ratio (2,5:2,6).

Despite isomers **158hh** and **168hh** being only partially separable, it was possible to isolate a small amount of each isomer for characterisation purposes.



Minor product
158hh

Orange solid, 12% yield; M. p. 189-191 °C; R_f 0.45 (1:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (td, J = 1.8, 0.6 Hz, 2H, H_b), 8.16 (ddd, J = 7.8, 1.8, 1.2 Hz, 2H, $H_{c/e}$), 7.76 (ddd, J = 7.8, 1.8, 1.2 Hz, 2H, $H_{c/e}$), 7.56 (td, J = 7.8, 0.6 Hz, 2H, H_d), 7.05 (s, 2H, H_a), 3.96 (s, 6H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.3 (C), 166.4 (C), 144.9 (C), 133.7 (CH), 133.5 (CH), 132.6 (C), 131.2 (CH), 130.8 (C), 130.3 (CH), 128.7 (CH), 52.4 (CH_3); ν_{max}/cm^{-1} 2958 w, 1722 v str, 1651 str, 1602 w, 1580 w, 1431 m, 1285 v str, 1233 m, 1184 m, 758 str; HRMS (NSI) calculated for $[M+H]^+$ 377.1020, $C_{22}H_{17}O_6$ found: 377.1021.

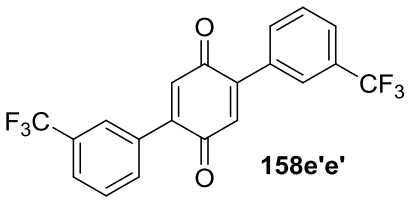


Major product
168hh

Orange crystalline solid, 13% yield; M. p. 164-168 °C; R_f 0.76 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (t, J = 1.5 Hz, 2H, H_b), 8.15 (dt, J = 7.8, 1.5 Hz, 2H, $H_{c/e}$), 7.72 (dt, J = 7.8, 1.5 Hz, 2H, $H_{c/e}$), 7.55 (t, J = 7.8 Hz, 2H, H_d), 7.00 (s, 2H, H_a), 3.95 (s, 6H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.0 (C), 185.4 (C), 166.4 (C), 145.5 (C), 133.7 (CH), 133.5 (C), 133.2 (CH), 131.1 (CH), 130.6 (C), 130.4 (CH), 128.7 (CH), 52.4 (CH_3); ν_{max}/cm^{-1} 2953 w, 1721 v str, 1650 str, 1603 w, 1439 m, 1293 v str, 1234 m, 1126 m, 750 m; HRMS (NSI) calculated for $[M+H]^+$ 377.1020, $C_{22}H_{17}O_6$ found: 377.1022.

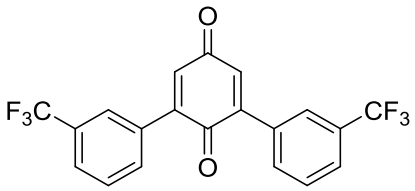
2,5-Bis-(3-trifluoromethylphenyl)-1,4-benzoquinone (158e'e') and **2,6-Bis-(3-trifluoromethylphenyl)-1,4-benzoquinone (168e'e')**

General procedure 3 was followed using an elevated temperature of 35 °C and an oxygen atmosphere. A second portion of boronic acid (0.150 mmol, 1.5 equiv.), 2,6-dichlorobenzoquinone (0.250 mmol, 2.5 equiv.) and $Pd(OTFA)_2$ (0.005 mmol, 5 mol%) was added after 24 h. After column chromatography evidence of reduced product was observed so additional oxidants ($FeCl_3$, 6 equiv. and 2,6-dichlorobenzoquinone, 2.5 equiv.) were added to the combined column fractions and left to stir at room temperature for 20 h. The 2,5 and 2,6 isomers were isolated in 60% yield (including a 5% impurity of mono arylated product due to coelution with the product) and a 1:1 ratio (**158e'e':168e'e'**).



158e'e'

Bright yellow amorphous solid, 30% yield includes <5% impurity of monoarylated product; R_f 0.38 (2:1 hexane: EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 – 7.79 (m, 2H, Ar-H), 7.79 – 7.70 (m, 4H, Ar-H), 7.68 – 7.56 (m, 2H, Ar-H), 7.04 (s, 2H, O=C-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.0 (C), 144.5 (C), 138.1 (C), 133.8 (CH), 132.6 (CH), 131.2 (C, q, J = 32.6 Hz), 129.2 (CH), 127.5 (C, q, J = 279.3 Hz), 126.9 (CH, q, J = 3.5 Hz), 126.1 (CH, q, J = 3.8 Hz); ν_{max}/cm^{-1} 2962 w, 1698 str, 1435 w, 1325 v str, 1164 str, 1118 v str, 1074 str, 803 m, 698 str; HRMS (APCI) calculated for $[M+H]^+$ 397.0658, $C_{20}H_{11}O_2F_6$ found: 397.0661.

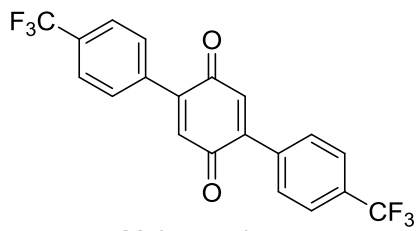


168e'e'

Bright orange amorphous solid, 30% yield; R_f 0.29 (2:1 hexane: EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 – 7.56 (m, 8H, Ar-H), 7.00 (s, 2H, O=C-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.6 (C), 185.0 (C), 145.1 (C), 138.4 (C), 133.6 (CH), 132.6 (CH), 131.1 (C, q, *J* = 32.6 Hz), 129.1 (CH), 126.8 (CH, q, *J* = 3.9 Hz), 126.2 (CH, q, *J* = 3.9 Hz), 123.7 (C, q, *J* = 272.5 Hz); ν_{max}/cm^{-1} 3226 w, 1698 str, 1497 w, 1441 w, 1324 v str, 1166 str, 1119 v str, 1060 str, 789 m, 702 m; HRMS (APCI) calculated for $[M+H]^+$ 397.0658, $C_{20}H_{11}O_2F_6$ found: 397.0658.

2,5-Bis-(4-trifluoromethylphenyl)-1,4-benzoquinone (158bb)[14]

General procedure 3 was followed using an elevated temperature of 35 °C to give **158bb**[14] as the major isomer. Some evidence of trace amounts of 2,6 isomer were observed however it was found to be unstable and impossible to isolate pure for characterisation.



Major product
158bb

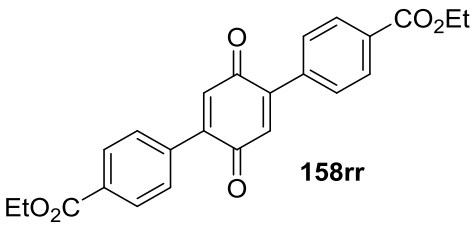
Bright yellow solid, 51% yield; M. p. 211-216 °C; R_f 0.61 (4:1 petroleum ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 4H, Ar-H), 7.66 (d, *J* = 8.3 Hz, 4H, Ar-H), 7.03 (s, 2H, O=C-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.0 (C), 144.6 (C), 135.6 (C), 133.9 (CH), 132.1 (C, q, *J* = 33.0 Hz), 129.7 (CH), 125.6 (CH, q, *J* = 3.7 Hz), 123.8 (C, q, *J* = 272.6 Hz); ν_{max}/cm^{-1} 2925 w, 1660 w, 1645 v str, 1609 w, 1410 w, 1328 v str, 1113 v str, 1069 v str, 910 str, 854 v str, 817 m, 701 m; HRMS (APCI) calculated for $[M+H]^+$ 397.0658, $C_{20}H_{11}O_2F_6$ found: 397.0651.

A crystal structure was also obtained of this product. This can be found in section 3.5.3.

2,5-Bis-(4-ethoxycarbonylphenyl)-1,4-benzoquinone (158rr)

General procedure 3 was followed using an elevated temperature of 35 °C and 3 equivalents (0.300 mmol) of 2,6-dichloro-1,4-benzoquinone. After 24 h, a second portion of boronic acid (0.051 mmol, 0.5 equiv.) and $Pd(OTFA)_2$ (0.005 mmol, 5 mol%) were added and after a further 7 h, $FeCl_3$ (0.272 mmol, 2.7 equiv.) was added as an additional oxidant. Upon purification by column chromatography, evidence of reduced

product was observed so 2,6-dichloro-1,4-benzoquinone (0.250 mol, 2.5 equiv.) was added to the fraction tubes and the resulting solution stirred for 72 h. After evaporation under reduced pressure, the residue was purified by column chromatography to give **158rr** in 25 % yield.

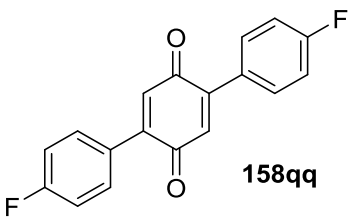


158rr

Yellow amorphous solid, 25% yield; R_f 0.31 (2:1 hexane: EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.6 Hz, 4H, Ar-H), 7.61 (d, J = 8.6 Hz, 4H, Ar-H), 6.85 (s, 2H, O=C-C<u>H</u>), 4.40 (q, J = 7.1 Hz, 4H, C<u>H$_2$</u>CH$_3$), 1.41 (t, J = 7.1 Hz, 6H, CH$_2$C<u>H$_3$</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (C), 149.5 (C), 142.0 (C), 130.1 (CH), 129.7 (C), 129.3 (CH), 129.0 (C), 117.0 (CH), 61.2 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 3431 br m, 2978 m, 1709 str, 1693 str, 1605 m, 1447 m, 1432 w, 1398 m, 1367 m, 1272 v str, 1102 str, 858 str, 774 str, 711 str; HRMS (APCI) calculated for $[M+H]^+$ 405.1333, $C_{24}H_{21}O_6$ found: 405.1333.

2,5-Bis-(4-fluorophenyl)-1,4-benzoquinone (158qq)[14, 57]

General procedure 3 was followed using an elevated temperature of 35 °C and adding a second portion of boronic acid (0.250 mmol, 2.5 equiv.), 2,6-dichlorobenzoquinone (0.251 mmol, 2.5 equiv.) and $Pd(OTFA)_2$ (0.005 mmol, 5 mol%) after 24 h to yield **158qq** as the major product (no trace of the 2,6 isomer was observed).

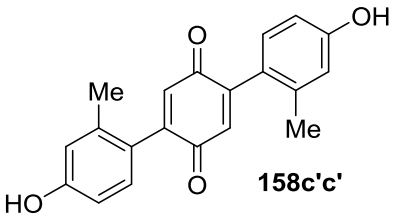


158qq

Bright yellow solid, 13% yield; M. p. 223-225 °C; R_f 0.69 (2:1 hexane: EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (dd, J = 8.8, 5.3 Hz, 4H, Ar-H), 7.16 (t, J = 8.8 Hz, 4H, Ar-H), 6.90 (s, 2H, O=C-C<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.2 (C), 163.9 (C-F, d, J = 251.2 Hz), 145.3 (C), 132.5 (CH), 131.4 (CH, d, J = 8.4 Hz), 129.0 (C), 115.7 (CH, d, J = 21.8 Hz); ν_{max}/cm^{-1} 3071 w, 1650 str, 1600 str, 1507 v str, 1411 w, 1300 m, 1230 v str, 1160 str, 835 str, 786 str.

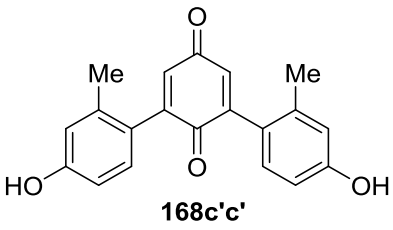
2,5-Bis-(4-hydroxy-2-methylphenyl)-1,4-benzoquinone (158c'c') and **2,6-Bis-(4-hydroxy-2-methylphenyl)-1,4-benzoquinone (168c'c')**

General procedure 3 was followed to give **158c'c'** and **168c'c'** in 41% combined yield and an approximate 1:1 ratio. The products were not easily separable but a small amount of material was isolated of each isomer for characterisation purposes.



158c'c'

Red solid, 15% yield; M. p. 65-67 °C; R_f 0.21 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.51 (s, 2H, O<u>H</u>), 7.28 – 6.92 (m, 2H, Ar-H), 6.90 – 6.54 (m, 6H, Ar-H and 2 × O=C-C<u>H</u>), 1.20 (s, 6H, C<u>H</u>$_3$); ^{13}C NMR (101 MHz, Acetone-d_6): δ = 187.6 (C), 159.2 (C), 148.7 (C), 139.0 (C), 135.3 (CH), 132.0 (CH), 125.9 (C), 117.9 (CH), 113.4 (CH), 20.8 (CH_3); ν_{max}/cm^{-1} 3305 br str, 2923 w, 1694 m, 1647 str, 1602 v str, 1498 m, 1454 m, 1295 m, 1230 str, 1188 v str, 990 m, 860 m, 752 m; HRMS (NSI) calculated for $[M+H]^+$ 321.1121, $C_{20}H_{17}O_4$ found: 321.1120.

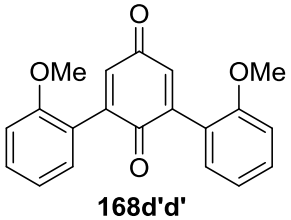


168c'c'

Red solid, 5% yield; M. p. 50-52 °C; R_f 0.18 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.49 (s, 2H, O<u>H</u>), 7.05 (d, *J* = 8.3 Hz, 2H, O=C-C<u>H</u>), 6.76 (d, *J* = 2.2 Hz, 2H, Ar-H), 6.75 – 6.68 (m, 4H, Ar-H), 1.20 (s, 6H, C<u>H</u>$_3$); ^{13}C NMR (101 MHz, Acetone-d_6): δ = 188.5 (C), 186.6 (C), 159.2 (C), 149.5 (C), 138.8 (C), 134.8 (CH), 131.9 (CH), 126.6 (C), 117.9 (CH), 113.5 (CH), 20.9 (CH_3); ν_{max}/cm^{-1} 3305 br str, 2923 m, 1698 w, 1645 v str, 1602 v str, 1498 m, 1454 m, 1289 v str, 1225 str, 1086 str, 822 m, 791 m; HRMS (APCI) calculated for $[M+H]^+$ 321.1121, $C_{20}H_{17}O_4$ found: 321.1128.

2,6-Bis-(2-methoxyphenyl)-1,4-benzoquinone (168d'd') and **2,5-Bis-(2-methoxyphenyl)-1,4-benzoquinone (158d'd')**

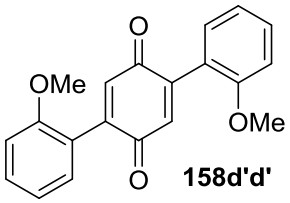
General procedure 3 was followed to yield **168d'd'** and **158d'd'** in an approximate 1:1 ratio.



168d'd'

Bright orange solid, 25% yield; M. p. 114-116 °C; R_f 0.32 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 2H, Ar-H), 7.21 (dd, *J* = 7.5, 1.8 Hz, 2H, Ar-H), 7.07 – 6.92 (m, 4H, Ar-H), 6.87 (s, 2H, O=C-C<u>H</u>), 3.81 (s, 6H, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 188.0 (C), 184.3 (C), 157.2 (C), 146.5 (C), 133.9 (CH), 131.0 (CH), 130.7 (CH), 123.3 (C), 120.6 (CH), 111.3 (CH), 55.8 (CH_3); ν_{max}/cm^{-1} 2936 w, 1647 str, 1598 str, 1576 m, 1489 str, 1453 m, 1249 str, 1128 m, 911 str, 823 w, 736 v str; HRMS (APCI) calculated for $[M+H]^+$ 321.1121, $C_{20}H_{17}O_4$ found: 321.1124.



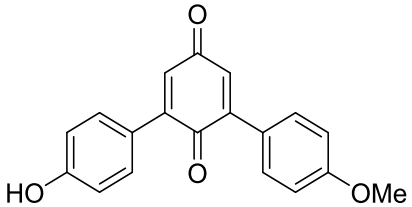
158d'd'

Bright orange solid, 28% yield; M. p. 208-210 °C; R_f 0.36 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 2H, Ar-H), 7.23 (dd, *J* = 7.5, 1.8 Hz, 2H, Ar-H), 7.09 – 6.95 (m, 4H, Ar-H), 6.91 (s, 2H, O=C-C<u>H</u>), 3.82 (s, 6H, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.1 (C), 157.3 (C), 145.3 (C), 134.9 (CH), 131.1 (CH), 130.6 (CH), 122.6 (C), 120.6 (CH), 111.3 (CH), 55.7 (CH_3); ν_{max}/cm^{-1} 2963 w, 1651 str, 1607 m, 1591 m, 1488 m, 1466 m, 1280 m, 913 str, 822 m, 791 m, 760 v str; HRMS (APCI) calculated for $[M+H]^+$ 321.1121, $C_{20}H_{17}O_4$ found: 321.1121.

Palladium(II)-catalysed functionalisation of monofunctionalised benzoquinone derivatives

2-(4-Hydroxyphenyl)-6-(4-methoxyphenyl)-1,4,benzoquinone (168cd) and **2-(4-Hydroxyphenyl)-5-(4-methoxyphenyl)-1,4,benzoquinone (158cd)**

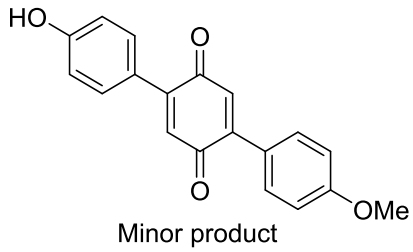
General procedure 4 was followed to give the products **168cd** and **158cd** in >10:1 ratio.



Major product
168cd

Dark brown solid, 73% yield; M. p. 143-145 °C; R_f 0.50 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.83 (s, 1H, O<u>H</u>), 7.59 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.52 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.03 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.94 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.84 (d, *J* = 2.7 Hz, 1H, O=C-C<u>H</u>), 6.82 (d, *J* = 2.7 Hz, 1H, O=C-C<u>H</u>), 3.87 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (101 MHz, Acetone-d_6): δ = 188.1 (C), 187.8 (C), 162.2 (C), 160.3 (C), 147.3 (C), 147.1 (C), 132.1 (CH), 132.0 (CH), 131.6 (CH), 131.2 (CH), 127.1 (C), 125.9 (C), 116.2 (CH), 114.7 (CH), 55.8 (CH_3); ν_{max}/cm^{-1} 3115 br str, 2928 str, 2840 m, 1635 v str, 1602 v str, 1583 v str, 1511 v str, 1444 str, 1236 v str, 1172 v str, 1028 str, 912 str, 827 str, 784 v str; HRMS (APCI) calculated for $[M+H]^+$ 307.0965, $C_{19}H_{15}O_4$ found: 307.0963.

A crystal structure was also obtained of this product. This can be found in section 3.5.3.

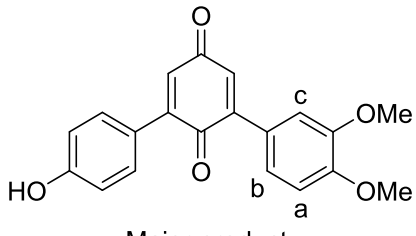


Minor product
158cd

Dark brown solid, <5% yield; M. p. 190-192 °C; R_f 0.56 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.85 (s, 1H, O<u>H</u>), 7.63 (d, J = 9.0 Hz, 2H, Ar-H), 7.55 (d, J = 8.9 Hz, 2H, Ar-H), 7.04 (d, J = 9.0 Hz, 2H, Ar-H), 6.94 (d, J = 8.9 Hz, 2H, Ar-H), 6.91 (s, 1H, O=C-C<u>H</u>), 6.89 (s, 1H, O=C-C<u>H</u>), 3.87 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (101 MHz, Acetone-d_6): δ = 188.0 (C), 187.9 (C), 162.2 (C), 160.3 (C), 145.6 (C), 145.4 (C), 132.4 (2 × CH), 132.1 (CH), 131.9 (CH), 126.1 (C), 125.0 (C), 116.2 (CH), 114.7 (CH), 55.8 (CH_3); ν_{max}/cm^{-1} 3387 br str, 2925 str, 2853 m, 1638 v str, 1600 v str, 1510 v str, 1441 m, 1247 v str, 1175 v str, 1028 str, 904 str, 835 str, 786 w; HRMS (APCI) calculated for $[M+H]^+$ 307.0965, $C_{19}H_{15}O_4$ found: 307.0966.

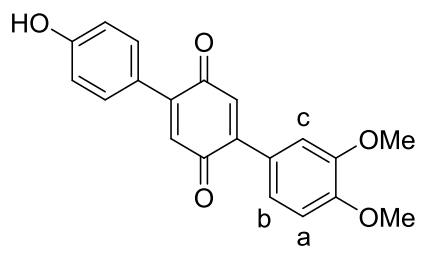
2-(4-Hydroxyphenyl)-6-(3,4-dimethoxyphenyl)-1,4,benzoquinone (168od) and **2-(4-Hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-1,4,benzoquinone (158od)**

General procedure 4 was followed to give the products **168od** and **158od** in an approximate 7:1 ratio.



Major product
168od

Dark red solid, 71% yield; M. p. 169-170 °C; R_f 0.43 (1:1 hexane:EtOAc); ^{1}H NMR (400 MHz, Acetone-d_6): δ = 8.84 (s, 1H, O<u>H</u>), 7.52 (d, J = 8.9 Hz, 2H, Ar-H), 7.25 (d, J = 2.1 Hz, 1H, H_c), 7.22 (dd, J = 8.4, 2.1 Hz, 1H, H_b), 7.04 (d, J = 8.4 Hz, 1H, H_a), 6.94 (d, J = 8.9 Hz, 2H, Ar-H), 6.87 (d, J = 2.7 Hz, 1H, O=C-C<u>H</u>), 6.82 (d, J = 2.7 Hz, 1H, O=C-C<u>H</u>), 3.87 (s, 3H, OC<u>H</u>$_3$), 3.87 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (101 MHz, Acetone-d_6): δ = 188.1 (C), 187.7 (C), 160.1 (C), 152.1 (C), 150.3 (C), 147.2 (C), 147.1 (C), 132.2 (CH), 131.7 (CH), 131.1 (CH), 127.2 (C), 125.9 (C), 123.8 (CH), 116.1 (CH), 114.2 (CH), 112.3 (CH), 56.3 (CH_3), 56.2 (CH_3); ν_{max}/cm^{-1} 3395 br, 2935 w, 1637 str, 1583 str, 1510 v str, 1440 w, 1415 w, 1251 v str, 1214 str, 1171 str, 1019 str, 817 w, 767 w; HRMS (NSI) calculated for $[M+H]^+$ 337.1071, $C_{20}H_{17}O_5$ found: 337.1073.

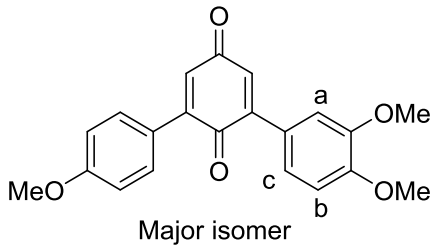


Minor product
158od

Dark red solid, 10% yield; M. p. 198-200 °C; R_f 0.40 (1:1 hexane:EtOAc); ^{1}H NMR (400 MHz, Acetone-d_6): δ = 8.86 (s, 1H, O<u>H</u>), 7.55 (d, J = 8.7 Hz, 2H, Ar-H), 7.29 – 7.24 (m, 2H, H_b and H_c), 7.05 (d, J = 9.0 Hz, 1H, H_a), 6.94 (d, J = 8.7 Hz, 2H, Ar-H), 6.94 (s, 1H, O=C-C<u>H</u>), 6.89 (s, 1H, O=C-C<u>H</u>), 3.88 (s, 6H, 2 × OC<u>H</u>$_3$); ^{13}C NMR (101 MHz, Acetone-d_6): δ = 188.1 (C), 187.9 (C), 160.3 (C), 152.2 (C), 150.1 (C), 145.5 (C), 145.4 (C), 132.5 (CH), 132.1 (CH), 132.0 (CH), 126.3 (C), 125.1 (C), 123.9 (CH), 116.2 (CH), 113.9 (CH), 112.3 (CH), 56.3 (CH_3), 56.2 (CH_3); ν_{max}/cm^{-1} 3449 br m, 2922 str, 1637 v str, 1588 str, 1512 v str, 1466 w, 1430 w, 1271 m, 1140 str, 1019 str, 818 m, 766 m; HRMS (NSI) calculated for $[M+H]^+$ 337.1071, $C_{20}H_{17}O_5$ found: 337.1074.

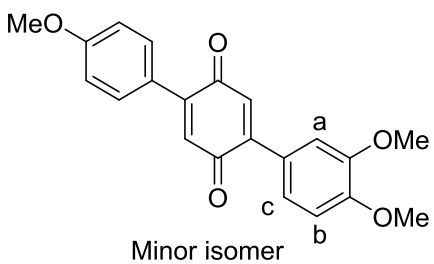
2-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-1,4,benzoquinone (168oc) and **2-(3,4-Dimethoxyphenyl)-5-(4-methoxyphenyl)-1,4,benzoquinone (158oc)**

General procedure 4 was followed to give the products **168oc** and **158oc** in an approximate 3:1 ratio.



Major isomer
168oc

Dark red solid, 65% yield; M. p. 140-142 °C; R_f 0.27 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.8 Hz, 2H, Ar-H), 7.16 (dd, J = 8.4, 2.1 Hz, 1H, H_c), 7.09 (d, J = 2.1 Hz, 1H, H_a), 6.98 (d, J = 8.8 Hz, 2H, Ar-H), 6.94 (d, J = 8.4 Hz, 1H, H_b), 6.87 (d, J = 2.7 Hz, 1H, O=C-C<u>H</u>), 6.86 (d, J = 2.7 Hz, 1H, O=C-C<u>H</u>), 3.93 (s, 3H, OC<u>H</u>$_3$), 3.92 (s, 3H, OC<u>H</u>$_3$), 3.86 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.6 (C), 186.9 (C), 161.2 (C), 150.8 (C), 148.8 (C), 145.9 (C), 145.7 (C), 131.4 (CH), 131.1 (CH), 130.9 (CH), 125.8 (C), 125.6 (C), 122.7 (CH), 114.0 (CH), 112.4 (CH), 110.9 (CH), 55.99 (CH_3), 55.97 (CH_3), 55.4 (CH_3); ν_{max}/cm^{-1} 3009 w, 2935 w, 2837 w, 1640 v str, 1601 str, 1510 v str, 1463 w, 1249 str, 1175 str, 1146 m, 1025 m; HRMS (APCI) calculated for $[M+H]^+$ 351.1227, $C_{21}H_{19}O_5$ found: 351.1226.

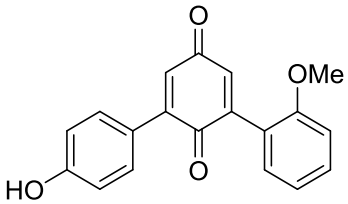


Minor isomer
158oc

Bright red solid, 21% yield; M. p. 156-158 °C; R_f 0.30 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.8 Hz, 2H, Ar-H), 7.21 (dd, J = 8.4, 2.1 Hz, 1H, H_c), 7.13 (d, J = 2.1 Hz, 1H, H_a), 6.99 (d, J = 8.8 Hz, 2H, Ar-H), 6.95 (d, J = 8.4 Hz, 1H, H_b), 6.92 (s, 1H, O=C-C<u>H</u>), 6.90 (s, 1H, O=C-C<u>H</u>), 3.94 (app. s, 6H, 2 × O<u>CH$_3$</u>), 3.87 (s, 3H, O<u>CH$_3$</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.4 (C × 2), 161.4 (C), 151.0 (C), 148.9 (C), 144.8 (C × 2), 131.8 (CH), 131.6 (CH), 130.9 (CH), 125.1 (C), 124.8 (C), 122.8 (CH), 114.1 (CH), 112.2 (CH), 111.0 (CH), 56.00 (CH_3), 55.98 (CH_3), 55.0 (CH_3); ν_{max}/cm^{-1} 3003 w, 2935 w, 2837 w, 1645 v str, 1601 str, 1588 str, 1510 v str, 1463 w, 1259 str, 1175 str, 1145 m, 1025 m; HRMS (APCI) calculated for $[M+H]^+$ 351.1227, $C_{21}H_{19}O_5$ found: 351.1226.

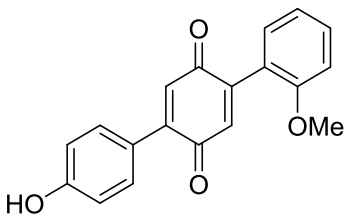
2-(4-Hydroxyphenyl)-6-(2-methoxyphenyl)-1,4,benzoquinone (168dd') and **2-(4-Hydroxyphenyl)-5-(2-methoxyphenyl)-1,4,benzoquinone (158dd')**

General procedure 4 was followed to give the products **168dd'** and **158dd'** in an approximate 5:4 ratio.



Major product
168dd'

Dark red solid, 50% yield; M. p. 178-181 °C; R_f 0.19 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.86 (s, 1H, O<u>H</u>), 7.51 (d, J = 8.7 Hz, 2H, Ar-H), 7.45 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H, Ar-H), 7.32 (dd, J = 7.5, 1.8 Hz, 1H, Ar-H), 7.12 (dd, J = 8.3, 1.0 Hz, 1H, Ar-H), 7.04 (td, J = 7.5, 1.0 Hz, 1H, Ar-H), 6.94 (d, J = 8.7 Hz, 2H, Ar-H), 6.86 (d, J = 2.7 Hz, 1H, O=C-C<u>H</u>), 6.77 (d, J = 2.7 Hz, 1H, O=C-C<u>H</u>), 3.83 (s, 3H, O<u>CH$_3$</u>); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 187.9 (C), 186.6 (C), 160.3 (C), 158.2 (C), 148.1 (C), 147.3 (C), 134.1 (CH), 132.0 (CH), 131.9 (CH), 131.2 (CH), 130.4 (CH), 125.7 (C), 124.9 (C), 121.4 (CH), 116.2 (CH), 112.2 (CH), 56.2 (CH_3); ν_{max}/cm^{-1} 3255 br, 2952 w, 1664 m, 1637 str, 1571 str, 1511 m, 1275 str, 1229 v str, 1174 m, 908 str, 743 str; HRMS (NSI) calculated for $[M+H]^+$ 307.0965, $C_{19}H_{15}O_4$ found: 307.0968.

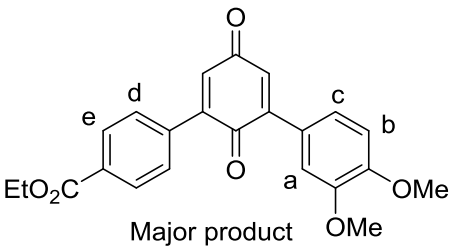


Minor product
158dd'

Red solid, 41% yield; M. p. 207-209 °C; R_f 0.23 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.85 (s, 1H, O<u>H</u>), 7.55 (d, J = 8.3 Hz, 2H, Ar-H), 7.49 – 7.38 (m, 1H, Ar-H), 7.27 (dd, J = 7.5, 1.7 Hz, 1H, Ar-H), 7.11 (d, J = 8.3 Hz, 1H, Ar-H), 7.06 – 7.00 (m, 1H, Ar-H), 6.95 (d, J = 8.3 Hz, 2H, Ar-H), 6.90 (d, J = 0.7 Hz, 1H, O=C-C<u>H</u>), 6.84 (d, J = 0.7 Hz, 1H, O=C-C<u>H</u>), 3.80 (d, J = 0.7 Hz, 3H, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 188.1 (C), 186.4 (C), 158.4 (C), 146.4 (C), 145.6 (C), 135.5 (CH), 134.2 (C), 132.1 (CH), 131.8 (CH), 131.7 (CH), 131.4 (CH), 125.1 (C), 123.9 (C), 121.2 (CH), 116.2 (CH), 112.3 (CH), 56.1 (CH_3); ν_{max}/cm^{-1} 3423 br, 2922 w, 1635 v str, 1588 v str, 1514 v str, 1437 m, 1248 v str, 1173 v str, 763 v str, 753 str; HRMS (NSI) calculated for $[M+H]^+$ 307.0965, $C_{19}H_{15}O_4$ found: 307.0968.

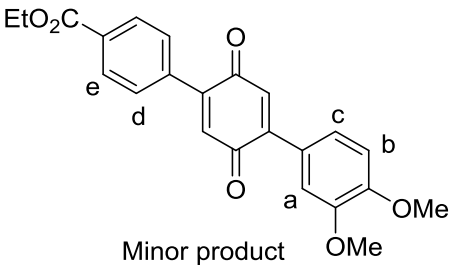
2-(4-Ethoxycarbonylphenyl)-6-(3,4-dimethoxyphenyl)-1,4,benzoquinone (168ro) and **2-(4-Ethoxycarbonylphenyl)-5-(3,4-dimethoxyphenyl)-1,4,benzoquinone (158ro)**

General procedure 4 was followed to give the products **168ro** and **158ro** in an approximate 3:1 ratio. See section 3.5.3 for the procedure used to differentiate between the 2,5 and 2,6 isomers.



Major product
168ro

Black solid, 48% yield; M. p. 148-150 °C; R_f 0.30 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.7 Hz, 2H, H_e), 7.58 (d, J = 8.7 Hz, 2H, H_d), 7.17 (dd, J = 8.4, 2.1 Hz, 1H, H_c), 7.09 (d, J = 2.1 Hz, 1H, H_a), 7.00 – 6.90 (m, 3H, 2 × O=C-C<u>H</u>, H_b), 4.41 (q, J = 7.1 Hz, 2H, C<u>H</u>$_2$CH$_3$), 3.94 (s, 3H, OC<u>H</u>$_3$), 3.93 (s, 3H, OC<u>H</u>$_3$), 1.42 (t, J = 7.1 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.2 (C), 186.0 (C), 166.0 (C), 151.1 (C), 148.9 (C), 145.8 (C), 145.7 (C), 137.5 (C), 133.4 (CH), 131.6 (C), 131.4 (CH), 129.5 (CH), 129.3 (CH), 125.5 (C), 122.9 (CH), 112.3 (CH), 111.0 (CH), 61.3 (CH_2), 56.02 (CH_3), 55.99 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} 2935 w, 1715 str, 1643 v str, 1513 str, 1464 m, 1257 v str, 1100 v str, 1022 v str, 917 w, 748 v str, 706 m; HRMS (APCI) calculated for $[M+H]^+$ 393.1333, $C_{23}H_{21}O_6$ found: 393.1328.

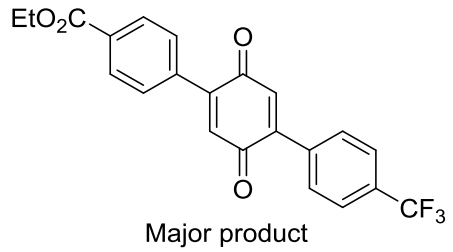


Minor product
158ro

Black solid, 16% yield; M. p. 186-188 °C; R_f 0.33 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.4 Hz, 2H, H_e), 7.61 (d, J = 8.4 Hz, 2H, H_d), 7.22 (dd, J = 8.4, 2.1 Hz, 1H, H_c), 7.13 (d, J = 2.1 Hz, 1H, H_a), 7.01 – 6.93 (m, 3H, 2 × O=C-C<u>H</u>, H_b), 4.41 (q, J = 7.1 Hz, 2H, C<u>H</u>$_2$CH$_3$), 3.95 (s, 3H, OC<u>H</u>$_3$), 3.94 (s, 3H, OC<u>H</u>$_3$), 1.42 (t, J = 7.1 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.2 (C), 186.4 (C), 166.0 (C), 151.2 (C), 149.0 (C), 145.0 (C), 144.7 (C), 136.7 (C), 133.9 (CH), 131.7 (C), 131.6 (CH), 129.6 (CH), 129.3 (CH), 124.8 (C), 122.9 (CH), 112.6 (CH), 111.1 (CH), 61.3 (CH_2), 56.03 (CH_3), 56.01 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} 2934 w, 1706 v str, 1644 v str, 1587 m, 1516 str, 1443 m, 1287 v str, 1268 v str, 1105 v str, 1022 v str, 910 str, 762 m, 701 m; HRMS (APCI) calculated for $[M+H]^+$ 393.1333, $C_{23}H_{21}O_6$ found: 393.1328.

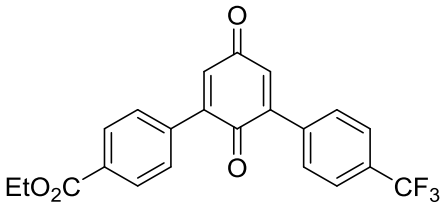
2-(4-Ethoxycarbonylphenyl)-5-(4-trifluoromethylphenyl)-1,4,benzoquinone (158rb) and **2-(4-Ethoxycarbonylphenyl)-6-(4-trifluoromethylphenyl)-1,4,benzoquinone (168rb)**

General procedure 4 was followed to give the products **158rb** and **168rb** in an approximate 10:1 ratio.



Major product
158rb

Bright yellow amorphous solid, 47% yield; R_f 0.43 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.6 Hz, 2H, Ar-H), 7.74 (d, J = 8.3 Hz, 2H, Ar-H), 7.66 (d, J = 8.3 Hz, 2H, Ar-H), 7.62 (d, J = 8.6 Hz, 2H, Ar-H), 7.04 (s, 1H, O=C-C<u>H</u>), 7.02 (s, 1H, O=C-C<u>H</u>), 4.42 (q, J = 7.1 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.42 (t, J = 7.1 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.10 (C), 186.06 (C), 165.9 (C), 145.0 (C), 144.5 (C), 136.4 (C), 135.7 (C), 134.0 (CH), 133.7 (CH), 132.0 (C. q, J = 33.4 Hz), 132.0 (C), 129.7 (2 × CH), 129.3 (CH), 125.5 (CH, q, J = 3.9 Hz), 123.8 (C, q, J = 271.6 Hz), 61.3 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 2924 w, 1723 v str, 1642 v str, 1326 str, 1278 str, 1125 v str, 1107 v str, 1069 v str, 909 v str, 713 str; HRMS (APCI) calculated for $[M+H]^+$ 401.0995, $C_{22}H_{16}F_3O_4$ found: 401.0995.

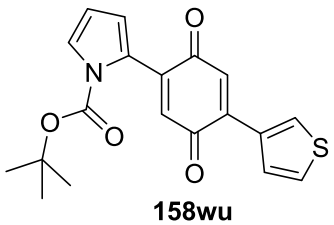


Minor product
168rb

Pale yellow amorphous solid, <5% yield; R_f 0.36 (5:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.5 Hz, 2H, Ar-H), 7.73 (d, J = 8.2 Hz, 2H, Ar-H), 7.63 (d, J = 8.2 Hz, 2H, Ar-H), 7.58 (d, J = 8.5 Hz, 2H, Ar-H), 6.99 (d, J = 2.6 Hz, 1H, O=C-C<u>H</u>), 6.97 (d, J = 2.6 Hz, 1H, O=C-C<u>H</u>), 4.41 (q, J = 7.1 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.42 (t, J = 7.1 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.8 (C), 185.1 (C), 165.9 (C), 145.6 (C), 145.3 (C), 137.0 (C), 136.4 (C), 133.6 (CH), 133.5 (CH), 131.9 (C, q, J = 37.9 Hz), 131.9 (C), 129.8 (CH), 129.6 (CH), 129.4 (CH), 125.46 (CH, q, J = 3.9 Hz), 124.8 (C, q, J = 271.6 Hz), 61.3 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 2924 w, 2855 str, 1715 str, 1609 w, 1457 w, 1325 v str, 1278 str, 1124 v str, 1068 v str, 843 w, 758 m; HRMS (APCI) calculated for $[M+H]^+$ 401.0995, $C_{22}H_{16}F_3O_4$ found: 401.0995.

2-(1-(*tert*-Butoxycarbonyl)-2-pyrrolyl)-5-(3-thienyl)-1,4,benzoquinone (158wu)

General procedure 4 was followed, using 2.5 equivalents of 3-thienyl boronic acid to give the 2,5 isomer **158wu**. Another product, believed to be the 2,6 isomer was observed but only in trace amounts.

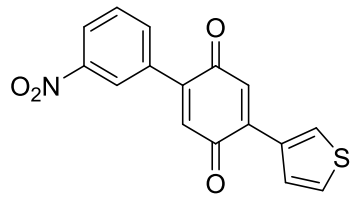


158wu

Red solid, 74% yield; M. p. 125-127 °C; R_f 0.50 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 2.8, 1.5 Hz, 1H, HetAr-H), 7.42 (dd, J = 3.4, 1.7 Hz, 1H, HetAr-H), 7.41 – 7.37 (m, 2H, HetAr-H), 6.99 (s, 1H, O=C-C<u>H</u>), 6.78 (s, 1H, O=C-C<u>H</u>), 6.41 (dd, J = 3.4, 1.7 Hz, 1H, HetAr-H), 6.26 (t, J = 3.4 Hz, 1H, HetAr-H), 1.52 (s, 9H, (C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.1 (C), 186.3 (C), 148.7 (C), 141.2 (C), 139.3 (C), 133.0 (C), 130.8 (CH), 130.2 (CH), 129.7 (CH), 126.9 (CH), 126.5 (C), 125.9 (CH), 125.0 (CH), 117.0 (CH), 111.1 (CH), 84.7 (C), 27.9 (CH_3); ν_{max}/cm^{-1} 2979 w, 1744 v str, 1655 v str, 1587 str, 1474 w, 1405 w, 1315 v str, 1223 m, 1136 v str, 848 w, 734 w; HRMS (NSI) calculated for $[M+H]^+$ 356.0951, $C_{19}H_{18}O_4NS$ found: 356.0954.

2-(3-Nitrophenyl)-5-(3-thienyl)-1,4,benzoquinone (158iu)

General procedure 4 was followed, using 2.5 equivalents of 3-thienyl boronic acid and $FeCl_3$ (1.25 equiv.) was added for 1 h at the end of the reaction. Column chromatography yielded the 2,5 isomer **158iu** as the major product but evidence of reduced product was observed following washing of the column with ethyl acetate. $FeCl_3$ (2.5 equiv.), was added as an additional oxidant to the column wash and left to stir at room temperature for 18 h, after which the solution was evaporated under reduced pressure and purified by column chromatography to yield further 2,5 product. Another product, believed to be the 2,6 isomer was observed but only in trace amounts.

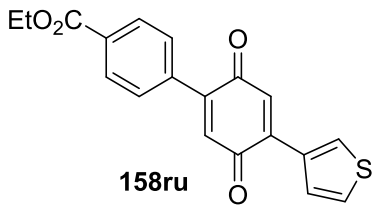


158iu

Red solid, 42% yield; M. p. 175-178 °C; R_f 0.27 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 – 8.41 (m, 1H, Ar-H), 8.36 – 8.31 (m, 1H, Ar-H), 8.23 – 8.21 (m, 1H, HetAr-H), 7.90 – 7.86 (m, 1H, Ar-H), 7.70 – 7.63 (m, 1H, Ar-H), 7.45 – 7.43 (m, 2H, HetAr-H), 7.08 (s, 1H, O=C-C<u>H</u>), 7.01 (s, 1H, O=C-C<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.6 (C), 186.2 (C), 148.3 (C), 143.1 (C), 139.3 (C), 135.2 (CH), 134.3 (CH), 134.0 (C), 132.3 (C), 130.4 (CH), 130.1 (CH), 129.6 (CH), 126.7 (CH), 126.4 (CH), 124.6 (CH), 124.3 (CH); ν_{max}/cm^{-1} 3107 w, 2925 w, 1650 v str, 1583 w, 1528 v str, 1347 str, 1220 w, 1158 w, 906 w, 730 w; HRMS (APCI) calculated for $[M+H]^+$ 312.0325, $C_{16}H_{10}O_4NS$ found: 312.0327.

2-(4-Ethoxycarbonylphenyl)-5-(3-thienyl)-1,4,benzoquinone (158ru)

General procedure 4 was followed to give **158ru** as the major product. Another product, believed to be the 2,6 isomer was observed but only in trace amounts.



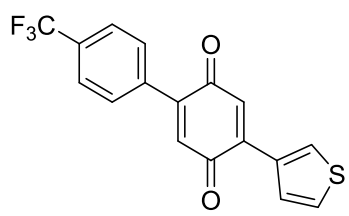
158ru

Red solid, 34% yield; M. p. 144-146 °C; R_f 0.26 (3:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (dd, J = 2.7, 1.6 Hz, 1H, HetAr-H), 8.12 (d, J = 8.6 Hz, 2H, Ar-H), 7.61 (d, J = 8.6 Hz, 2H, Ar-H), 7.44 – 7.41 (m, 2H, HetAr-H), 7.05 (s, 1H, O=C-C<u>H</u>), 6.96 (s, 1H, O=C-C<u>H</u>), 4.41 (q, J = 7.2 Hz, 2H, C<u>H$_2$</u>CH$_3$), 1.41 (t, J = 7.2 Hz, 3H, CH$_2$C<u>H$_3$</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.9 (C), 186.7 (C), 166.0 (C), 144.6 (C), 139.2 (C), 136.7 (C), 134.0 (CH), 132.6 (C), 131.9 (C), 130.4 (CH), 130.0 (CH), 129.6 (CH), 129.3 (CH), 126.8 (CH), 126.2 (CH), 61.2 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 3105 w, 2981 w, 1717 v str, 1652 v str, 1640 v str,

1583 w, 1409 w, 1277 v str, 1107 str, 911 w, 792 w, 723 m; HRMS (APCI) calculated for $[M+H_2O-H]^+$ 355.0635, $C_{19}H_{15}O_5S$ found: 355.0629.

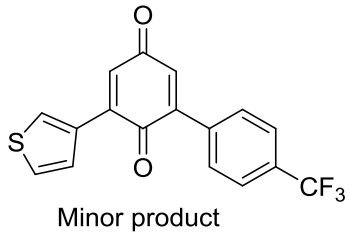
2-(4-Trifluoromethylphenyl)-5-(3-thienyl)-1,4,benzoquinone (158ub) and **2-(4-Trifluoromethylphenyl)-6-(3-thienyl)-1,4,benzoquinone (168ub)**

General procedure 4 was followed, using 2.5 equivalents of 3-thienyl boronic acid and adding $FeCl_3$ (1.4 equiv.) for 1 h at the end of the reaction to give **158ub** and **168ub** in an approximate 3:2 ratio. The minor isomer **168ub** was isolated but could not be sufficiently purified. Additionally, due to decomposition a ^{13}C NMR spectrum could not be obtained.



Major product
158ub

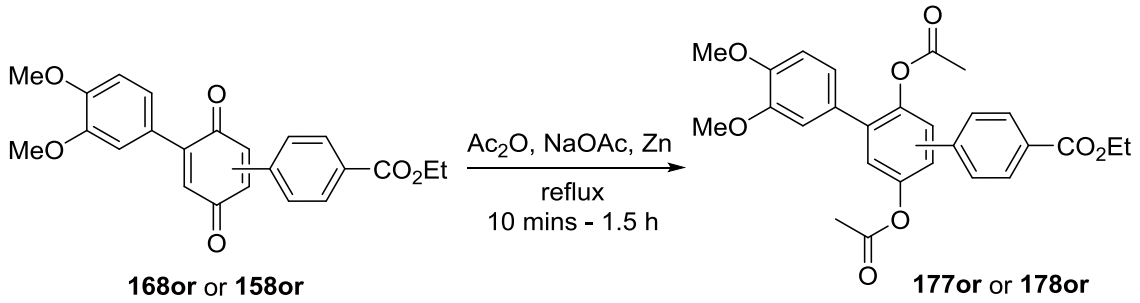
Yellow amorphous solid, 31% yield; R_f 0.74 (2:1 hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 – 8.17 (m, 1H, HetAr-H), 7.73 (d, J = 8.3 Hz, 2H, Ar-H), 7.65 (d, J = 8.3 Hz, 2H, Ar-H), 7.48 – 7.38 (m, 2H, HetAr-H), 7.06 (s, 1H, O=C-C<u>H</u>), 6.95 (s, 1H, O=C-C<u>H</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.9 (C), 186.6 (C), 144.1 (C), 139.2 (C), 135.9 (C), 134.1 (CH), 132.4 (C), 131.9 (q, J = 28.2 Hz, C), 130.2 (CH), 129.7 (CH ×2), 126.7 (CH), 126.3 (CH), 125.4 (q, J = 3.9 Hz, CH), 123.0 (q, J = 167.7 Hz, C); ν_{max}/cm^{-1} 2929 w, 1641 v str, 1327 v str, 1168 w, 1124 str, 1071 str, 848 w; HRMS (APCI) calculated for $[M+H]^+$ 335.0348, $C_{17}H_{10}F_3O_2S$ found: 335.0347.



Minor product
168ub

Yellow amorphous solid, 23% yield; R_f 0.58 (2:1 hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (1 H, t, J = 2.1 Hz, HetAr-H), 7.73 (2 H, d, J = 8.0 Hz, Ar-H), 7.61 (2 H, d, J = 8.0 Hz, Ar-H), 7.44 – 7.38 (2 H, m, HetAr-H), 7.03 (1 H, d, J = 2.6 Hz, O=C-C<u>H</u>), 6.91 (1 H, d, J = 2.6 Hz, O=C-C<u>H</u>); ν_{max}/cm^{-1} 2924 m, 1668 w, 1647 str, 1585 w, 1410 w, 1324 v str, 1168 m, 1127 str, 1068 str, 845 w; HRMS (APCI) calculated for $[M+H]^+$ 335.0348, $C_{17}H_{10}F_3O_2S$ found: 335.0350.

Diacetylation of 2,5- and 2,6-diaryl-1,4-hydroquinones[32]



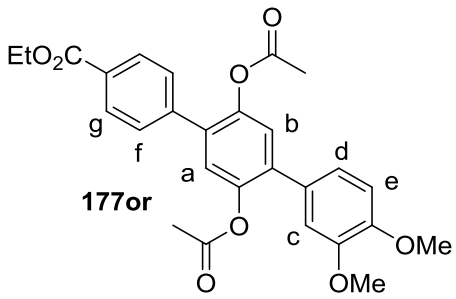
168or or **158or** **177or** or **178or**

General procedure for diacetylation:

Heterodifunctionalised benzoquinones **168or** or **158or** (1 equiv.), zinc (5 equiv.) and anhydrous NaOAc (2 equiv.) were added to a flask followed by acetic anhydride (0.096 M) and the solution was heated to reflux. Upon completion, the solution was filtered through glass wool and the filtrate washed with acetic acid. Water (5 mL) and EtOAc (5 mL) were then added, the layers were separated and the aqueous phase washed with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 × 5 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (5:1 → 1:1 pentane:Et_2O) to yield the product.

Ethyl 4-[2,5-bis(acetyloxy)-4-(3,4-dimethoxyphenyl)phenyl]benzoate (177or)

Compound **158or** (0.0133 mmol) was diacetylated using the aforementioned procedure[32] to give **177or** in a 78% yield.



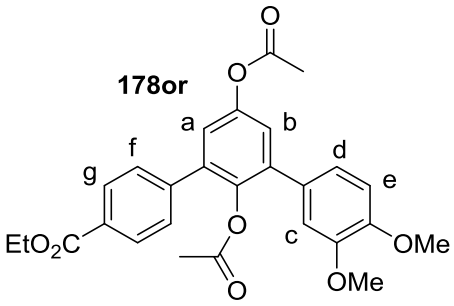
177or

Yellow amorphous solid, 78% yield; R_f 0.23 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.6 Hz, 2H, H_g), 7.53 (d, J = 8.6 Hz, 2H, H_f), 7.20 (s, 1H, $H_{a/b}$), 7.19 (s, 1H, $H_{a/b}$), 7.02 (dd, J = 8.2, 2.0 Hz, 1H, H_d), 6.99 (d, J = 2.0 Hz, 1H, H_c), 6.93 (d, J = 8.2 Hz, 1H, H_e), 4.41 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.93 (s, 3H, $OC\underline{H}_3$), 3.91 (s, 3H, $OC\underline{H}_3$), 2.13 (s, 3H, $C\underline{H}_3$), 2.11 (s, 3H, $C\underline{H}_3$), 1.42 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2 (C), 169.0 (C), 166.3 (C), 148.9 (C), 148.7 (C), 145.6 (C), 145.4 (C), 141.1 (C), 135.5 (C), 133.5 (C), 129.8 (C), 129.6 (CH), 129.0 (C), 128.8 (CH), 125.0 (CH), 124.8 (CH), 121.3 (CH), 111.9 (CH), 111.1 (CH), 61.1 (CH_2), 56.0 (CH_3), 55.9 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 14.4 (CH_3); ν_{max}/cm^{-1} 2929 w, 1761 str, 1714 str, 1608 w, 1513 w, 1488 w,

1367 str, 1274 str, 1199 v str, 1155 v str, 915 m, 860 w, 730 m; HRMS (APCI) calculated for $[M+H]^+$ 479.1700, $C_{27}H_{27}O_8$ found: 479.1695.

Ethyl 4-[2,5-bis(acetyloxy)-3-(3,4-dimethoxyphenyl)phenyl]benzoate (178or)

Compound **168or** (0.0201 mmol) was diacetylated using the aforementioned procedure[32] to give **178or** in a 76% yield.



Yellow amorphous solid, 76% yield; R_f 0.22 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.5 Hz, 2H, H_g), 7.52 (d, J = 8.5 Hz, 2H, H_f), 7.16 (d, J = 2.8 Hz, 1H, $H_{a/b}$), 7.12 (d, J = 2.8 Hz, 1H, $H_{a/b}$), 7.00 (dd, J = 8.1, 2.0 Hz, 1H, H_d), 6.97 (d, J = 2.0 Hz, 1H, H_c), 6.91 (d, J = 8.1 Hz, 1H, H_e), 4.40 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.92 (s, 3H, $OC\underline{H}_3$), 3.89 (s, 3H, $OC\underline{H}_3$), 2.32 (s, 3H, $C\underline{H}_3$), 1.82 (s, 3H, $C\underline{H}_3$), 1.41 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3 (C), 168.7 (C), 166.3 (C), 148.8 (C), 148.6 (C), 148.3 (C), 142.5 (C), 141.7 (C), 136.9 (C), 135.9 (C), 129.8 (C), 129.5 (CH), 129.5 (C), 128.9 (CH), 123.4 (CH), 122.3 (CH), 121.4 (CH), 112.0 (CH), 111.0 (CH), 61.1 (CH_2), 55.93 (CH_3), 55.88 (CH_3), 21.1 (CH_3), 20.6 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} 2933 w, 1762 str, 1713 str, 1608 w, 1516 str, 1441 w, 1367 str, 1273 str, 1174 v str, 1160 v str, 1022 str, 915 m, 864 w, 731 m; HRMS (APCI) calculated for $[M+H]^+$ 479.1700, $C_{27}H_{27}O_8$ found: 479.1698.

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Chapter 4: Palladium(II)-Catalysed Asymmetric Oxidative Heck Reactions on Cyclopentene-1,3-diones

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Chapter 4: Introduction

4.1 Background

Cyclopentenediones are ubiquitous in nature and exhibit a range of biological activities including antibacterial, antifungal, anti-inflammatory, cytostatic and enzyme inhibitory properties.[1] Around one hundred of these compounds have been reported to date, the majority of which have been isolated from plant sources. Within this class of compounds, a 2,2-disubstituted cyclopentene-1,3-dione moiety **183** is often present, for instance in natural products such as Madindoline A and B (**184** and **185**),[2-7] Similin A (**186**),[8] Involutone (**187**),[9-11] Ochroleucin A_1 (**188**)[12] and Preussidone (**189**) (Figure 9).[13]

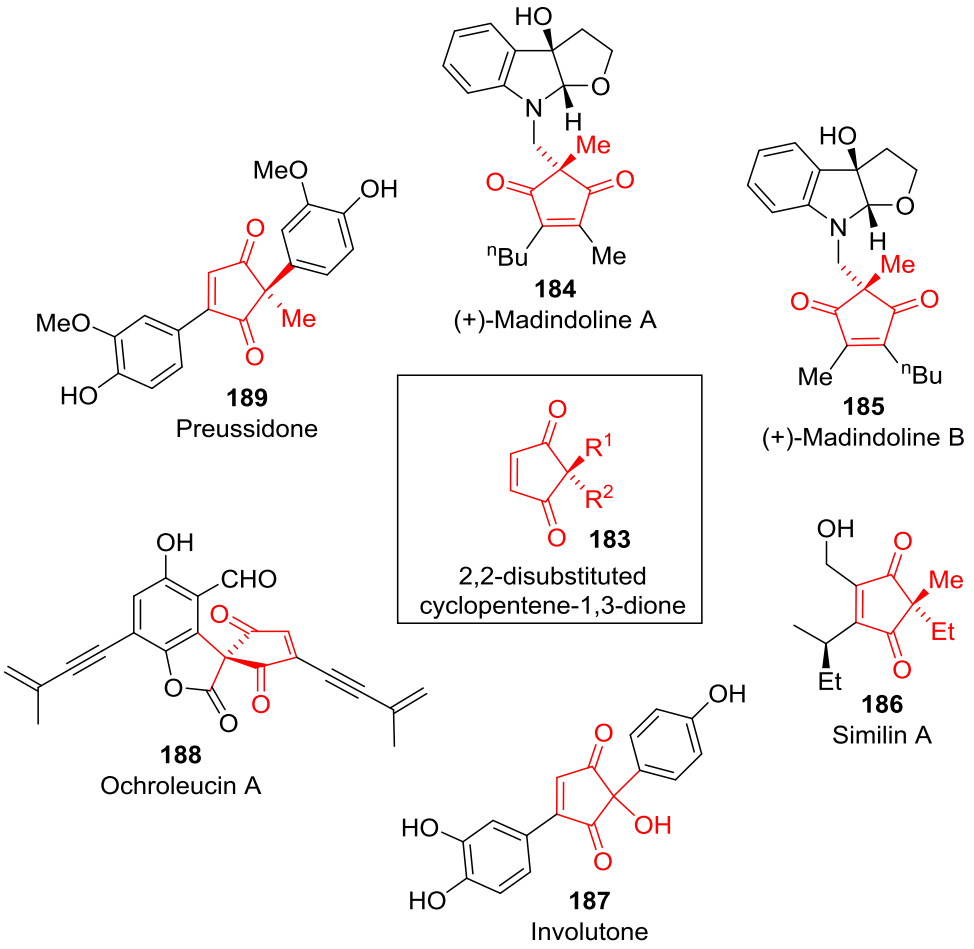


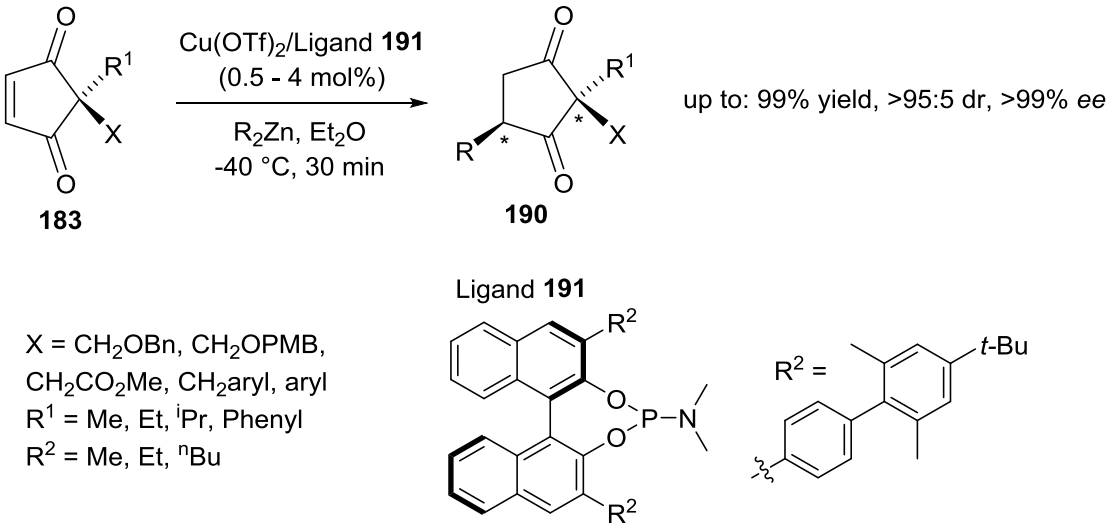
Figure 9: Biologically active natural products containing the 2,2-disubstituted cyclopentene-1,3-dione core **183**

Current synthetic routes to functionalised 2,2-disubstituted cyclopentene-1,3-diones **183** are lengthy[1] and given the prevalence of this moiety in natural products and the biological activity exhibited by these compounds, a direct synthetic route to access these structures would therefore be advantageous. On commencing the work outlined in this chapter, no direct syntheses of these compounds had been reported and therefore would be highly desirable. Additionally, given the challenge for synthetic chemists in forming all-carbon stereocentres,[14, 15] functionalising such compounds would provide a facile route to desymmetrise the prochiral centre, despite being remote from the reaction site. A Heck-type coupling method would therefore provide an ideal route to both functionalise the 2,2-disubstituted cyclopentene-1,3-dione core in addition to desymmetrising the all-carbon quaternary stereocentre in a one step process.

This review will touch on relevant literature examples using 2,2-disubstituted cyclopentene-1,3-diones in synthetic methodology in addition to relevant work reported in the literature during the course of this project.

4.1.1 Current methods to functionalise 2,2-disubstituted cyclopentene-1,3-diones

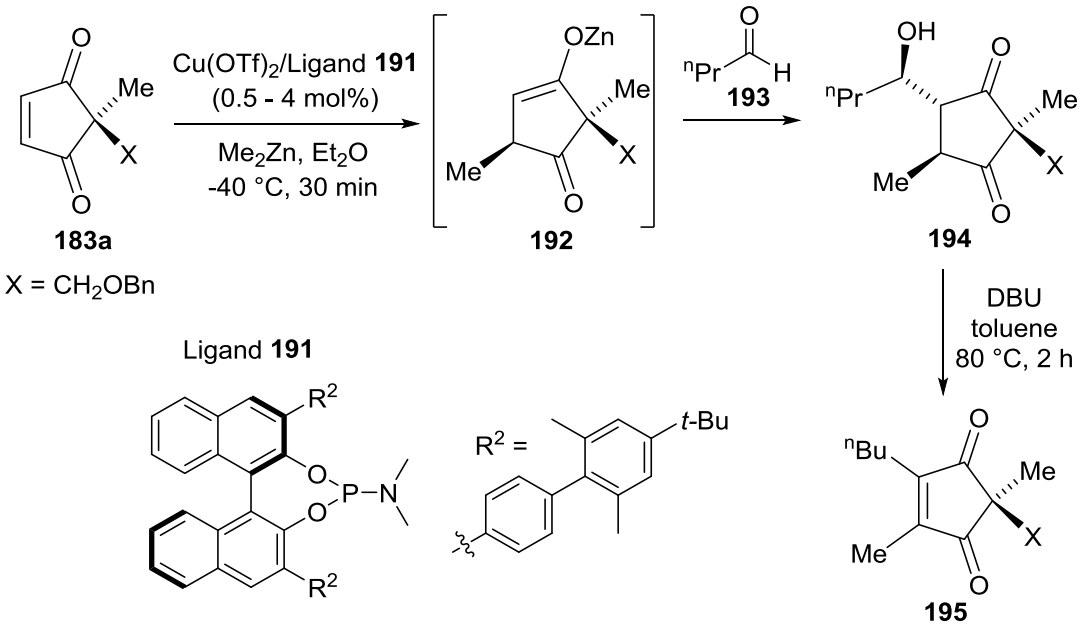
Investigations into the functionalisation of 2,2-disubstituted cyclopentene-1,3-diones **183** have primarily focussed on conjugate addition reactions. Mikami and co-workers have developed a copper(I)-catalysed asymmetric conjugate addition method in high yield and high enantioselectivity (Scheme 91).[16] Chiral copper-phosphoramidite catalysts with a loading as low as 0.5 mol% were used in an alkylation sequence using dialkylzinc reagents to access a variety of cyclopentane derivatives with a remote quaternary stereocentre.



Scheme 91: Copper(I)-catalysed enantioselective conjugate addition on 2,2-disubstituted cyclopentene-1,3-dione substrates

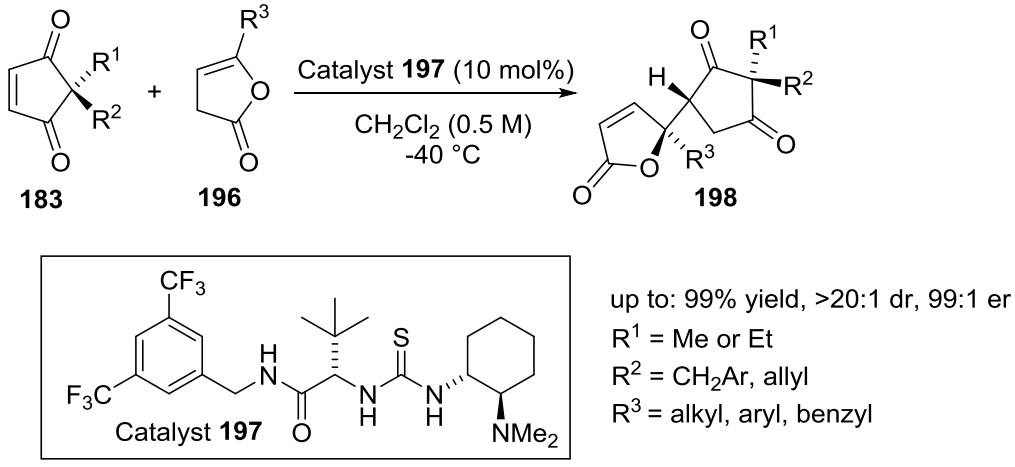
A variety of substituents at the 2 position on the cyclopentenedione core **183** were tolerated and the reaction afforded excellent yields (up to 99%) with a number of dialkyl zinc reagents. Excellent enantio- (>99% ee) and diastereoselectivities (>95:5 dr) were also obtained. However, obvious drawbacks to the methodology include the low temperature required, limited accessibility and cost of dialkyl zinc reagents, in addition to some functional groups not being tolerated.

Additionally, the methodology was expanded to synthesise a precursor to Madindolines (**195**, Scheme 92). The zinc enolate intermediate **192** was further reacted with an aldehyde **193** to afford a cyclopentane derivative bearing 4 chiral centres **194**. Elimination and isomerisation then regenerated the cyclopentenedione core and formed the Madindoline precursor **195**.



Scheme 92: Synthesis of a precursor to Madindolines

Mukherjee and coworkers have studied substituted cyclopentene-1,3-dione substrates and reported an enantioselective vinylogous nucleophilic addition using butenolides and thus desymmetrising the prochiral centre. Excellent diastereo- and enantioselectivities were obtained (Scheme 93).[17, 18]



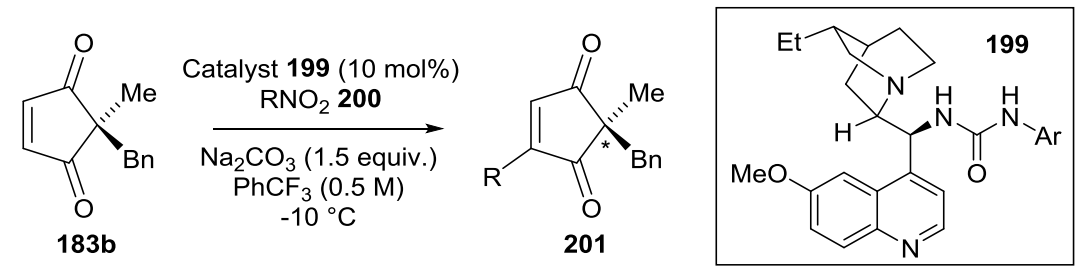
Scheme 93: Direct nucleophilic addition of butenolides to substituted cyclopentene-1,3-diones

Using amine-thiourea based catalysts **197**, a variety of 2,2-disubstituted cyclopentene-1,3-diones **183** bearing various functional groups at the 2 position were desymmetrised to afford cyclopentanedione products **198** bearing multiple stereocentres (one tertiary and two quaternary), including one outside of the cyclopentane scaffold. Yields were excellent (up to 99%) in addition to excellent diastereo- (>20:1 dr) and

enantioselectivity (99:1 er) being obtained. Investigations into the mechanism found that not only does the thiourea moiety of the catalyst induce selectivity, but additionally the amide side chain plays an important role in determining enantioselectivity.

The aforementioned work by Manna and Mukherjee was followed up by a study of a base-mediated organocatalytic enantioselective alkylation of 2,2-disubstituted cyclopentene-1,3-diones which was reported as the manuscript for this project[19] was being prepared (Scheme 94).[20] Also employing a bifunctional aminourea based catalyst as the chiral base **199**, functionalisation was achieved using nitroalkyl reagents **200** to yield substituted cyclopentenediones **201** in up to 92% yield and 97:3 er.

In this reaction, the base **199** deprotonates the nitroalkane **200** and the resulting nucleophile adds in a conjugate addition fashion to **183b**. Elimination of the NO_2 group then reforms the double bond in **201**.



R = Et, ^{n}Bu, Bn, CH_2aryl, $CH_2CH_2NR_2$, CH_2CH_2heterocycle

Scheme 94: Organocatalytic enantioselective alkylation of 2,2-disubstituted cyclopentene-1,3-diones

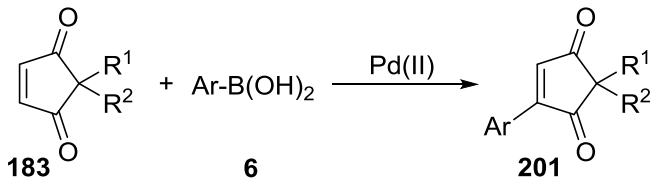
Although necessarily restricted to alkylations, a wide variety of functional groups were tolerated by the methodology both as substituents at the 2 position on the cyclopentene ring (benzyl, naphthyl, allyl) and as nucleophiles (CH_2CH_2-hydroxyl, -amide, -amine, -furan, -OTBS, -enone).

4.1.2 Conclusion

To conclude, the functionalisation of 2,2-disubstituted cyclopentene-1,3-diones is an area with much potential for further exploration. There are few examples in the literature of functionalisation of such substrates, despite their prevalence in natural products. Additionally, enantioselective functionalisation would be of great use in order to create all-carbon quaternary stereocentres in a direct and facile manner. To be able to use these substrates in Heck-type couplings would be a huge advancement in this area and open up further possibilities for synthetic routes to biologically active compounds.

4.2 Project aim

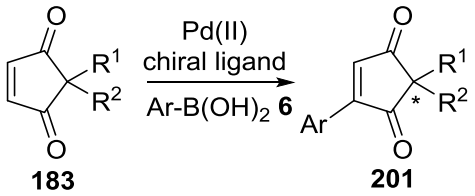
The Lee group has conducted extensive work on Pd(II)-catalysed reactions between cyclic enones and boronic acids, some of which is detailed in this thesis (see chapters 2 and 3).[21-23] During early studies in the Lee group on oxidative Heck reactions to cyclic enones, initial reactions on 2,2-disubstituted cyclopenten-1,3-dione substrates **183** indicated that the oxidative Heck product **201** was formed preferentially over the conjugate addition product.* Given the challenges in carrying out Heck-type reactions on cyclic enones, and few reported literature examples of functionalising such compounds (*vide supra*), further investigations were therefore worthwhile. With this in mind, the aim for this project was to build upon the initial promising results and develop an oxidative Heck reaction on 2,2-disubstituted cyclopenten-1,3-dione substrates **183** with a range of substituents on the cyclopentenedione core (R^1 and R^2) and boronic acid coupling partners **6** (Scheme 95).



Scheme 95: Development of a racemic oxidative Heck reaction on 2,2-disubstituted cyclopentene-1,3-dione substrates

Once the racemic reaction had been developed, our second aim was to develop an enantioselective oxidative Heck reaction with the aforementioned substrates (Scheme 96). By carrying out further optimisation where necessary and screening a number of chiral ligands, our aim was to establish an enantioselective protocol in order to desymmetrise the all-carbon quaternary centre in high yield and enantioselectivity. This second part of the project was the main focus of the author's work.

* Initial studies carried out by J. Jordan-Hore.



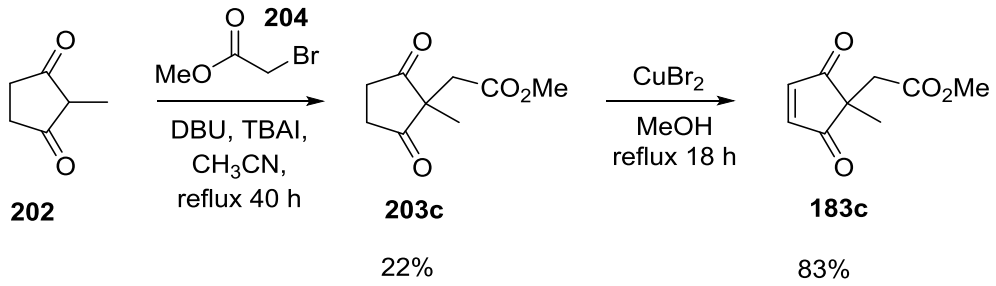
Scheme 96: Development of an enantioselective oxidative Heck reaction on 2,2-disubstituted cyclopentene-1,3-dione substrates

4.3 Development of a racemic oxidative Heck reaction on 2,2-disubstituted cyclopenten-1,3-diones

4.3.1 Substrate synthesis

The initial part of this project involved synthesising a library of substrates. This was carried out in collaboration with other Lee group members. Synthetic routes of substrates synthesised by the author are detailed below. Literature methods were followed for known compounds, or adapted where necessary in order to synthesise unknown substrates. One of two general synthetic routes was used depending on the substrate synthesised.

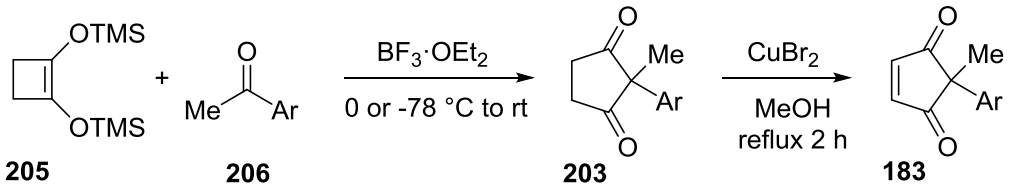
The first synthetic route was used to synthesise methyl 2-(1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate **183c** (Scheme 97) This methodology was taken from a literature procedure used for similar substrates.[16] Carrying out a simple S_N2 reaction with 2-methylcyclopentene-1,3-dione **202** and the appropriate alkyl bromide **204** yields the substrate precursor **203c**, albeit in 22% yield. Oxidation of this precursor **203c** using copper(II) bromide under reflux gave the desired product **183c** in 83% yield (Scheme 97).



Scheme 97: Synthesis of methyl 2-(1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate

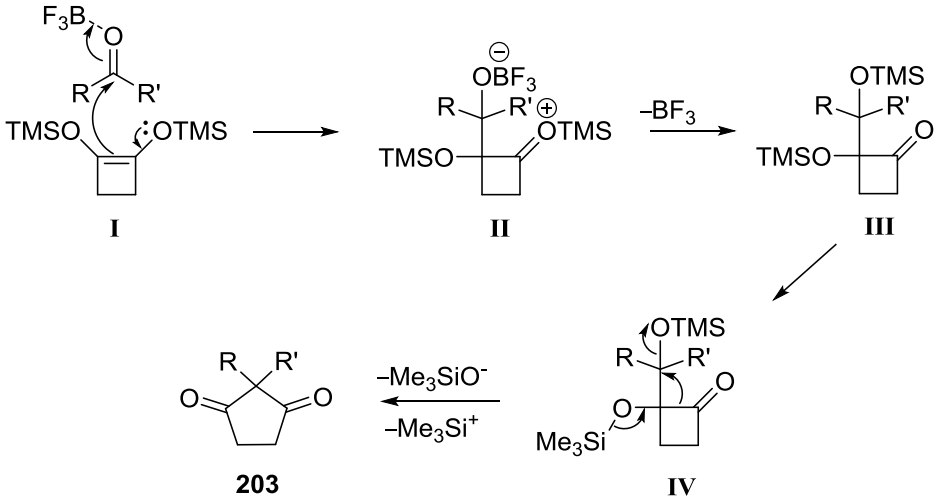
For those substrates which could not be synthesised by this method i.e. for aryl groups, an alternative synthetic route was adopted which was also taken from literature for synthesising similar substrates (Scheme 98).[16, 24] Using 1,2-bis(trimethylsiloxy)cyclobutene **205** as a starting material and reacting with the appropriate ketone **206** in the presence of a Lewis acid ($BF_3 \cdot OEt_2$) forms the cyclopentanedione precursor **203** of the desired substrate **183**. For substrates **183d** and **183e**, adding the reagents at 0 °C and warming the reaction mixture to room temperature was found to give reasonable yield (see Table 23).[16] However, this methodology was later altered and a slightly different literature procedure was adopted[24]

using a lower reaction temperature of –78 °C which was found to be more effective, particularly with more sterically hindered ketones (**183f-i**, see experimental section for more specific information). Oxidation of this precursor **203** was then carried out using copper(II) bromide to form the cyclopentenedione substrate **183**.



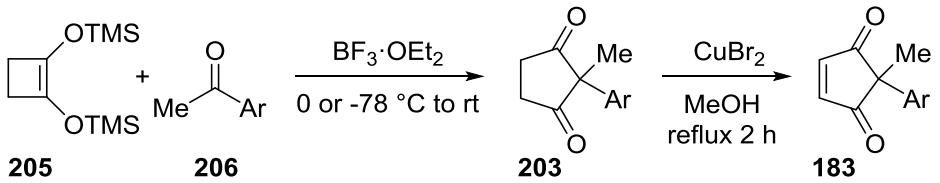
Scheme 98: General synthetic route for substrate synthesis

The mechanism for the synthesis of the substrate precursor **203** proceeds *via* a Mukaiyama-aldol reaction (**I** → **III**) followed by a semi-pinacol rearrangement (**IV** → **203**) as indicated in Scheme 99.[25]

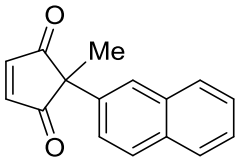
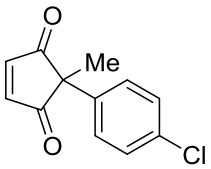
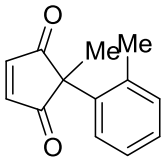
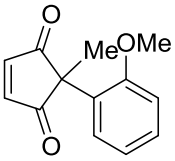
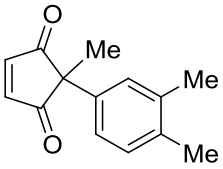
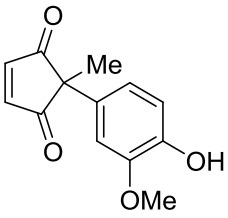


Scheme 99: Mechanism for the formation of substrate precursor **203**

The aforementioned synthetic route was used to synthesise a number of substrates (**183d-i**). Yields and reaction temperatures are shown in Table 23.



205 **206** **203** **183**

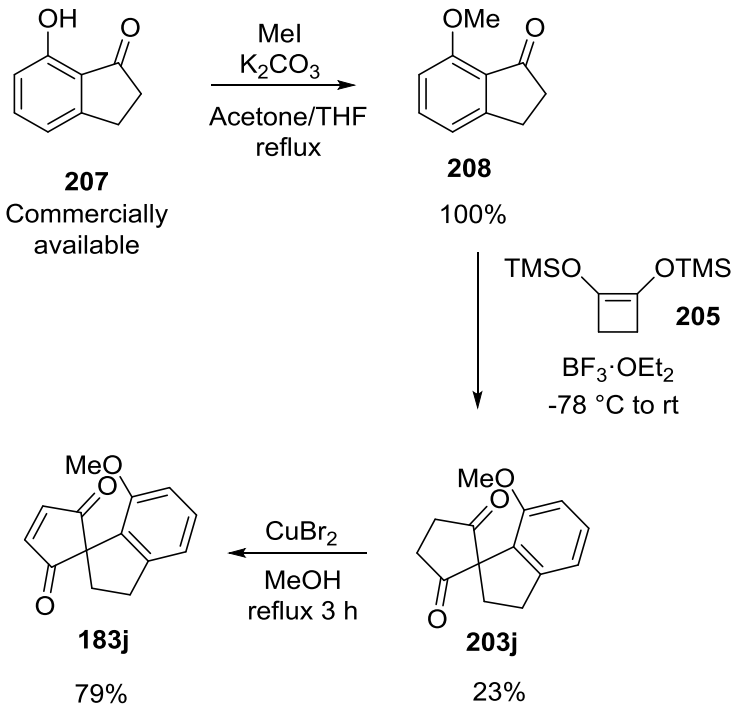
Entry	Substrate (183)	Temperature (step 1)	Yield 203 (%)[a] - step 1	Yield 183 (%)[a] - step 2
1		0 °C to rt	**203d** 57	**183d** 77
2		0 °C to rt	**203e** 45	**183e** 58
3		–78 °C to rt	**203f** 36	**183f** 79
4		–78 °C to rt	**203g** 34	**183g** 80
5		–78 °C to rt	**203h** 67	**183h** 75
6		–78 °C to rt	Crude product used for step 2	**183i** 16

[a]Isolated yields.

Table 23: Substrates synthesised for the oxidative Heck reaction on cyclopentenedione

Additionally a substrate with a spiro centre was synthesised using the synthetic route shown below (Scheme 100) which was also adapted from literature.[24] A simple

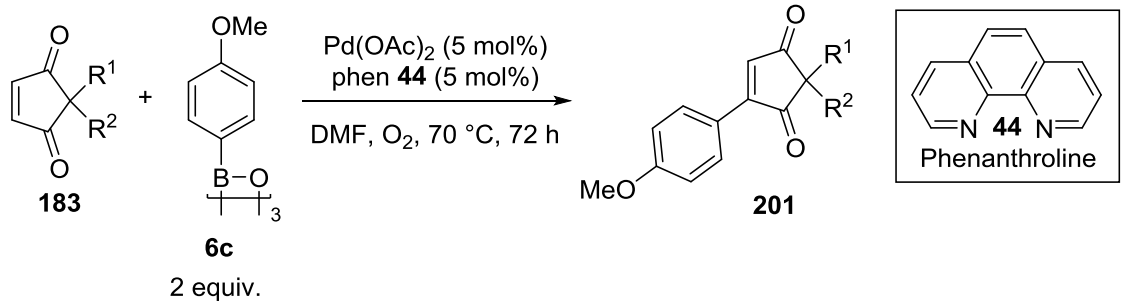
methylation formed the desired ketone **208** in quantitative yield. Reacting this with 1,2-bis(trimethylsiloxy)cyclobutene **205** formed the substrate precursor **203j** albeit in low yield (23%). The standard copper(II) bromide oxidation conditions used for other substrates then yielded the desired substrate **183j** in 79% yield.



Scheme 100: Synthesis of 7'-methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione

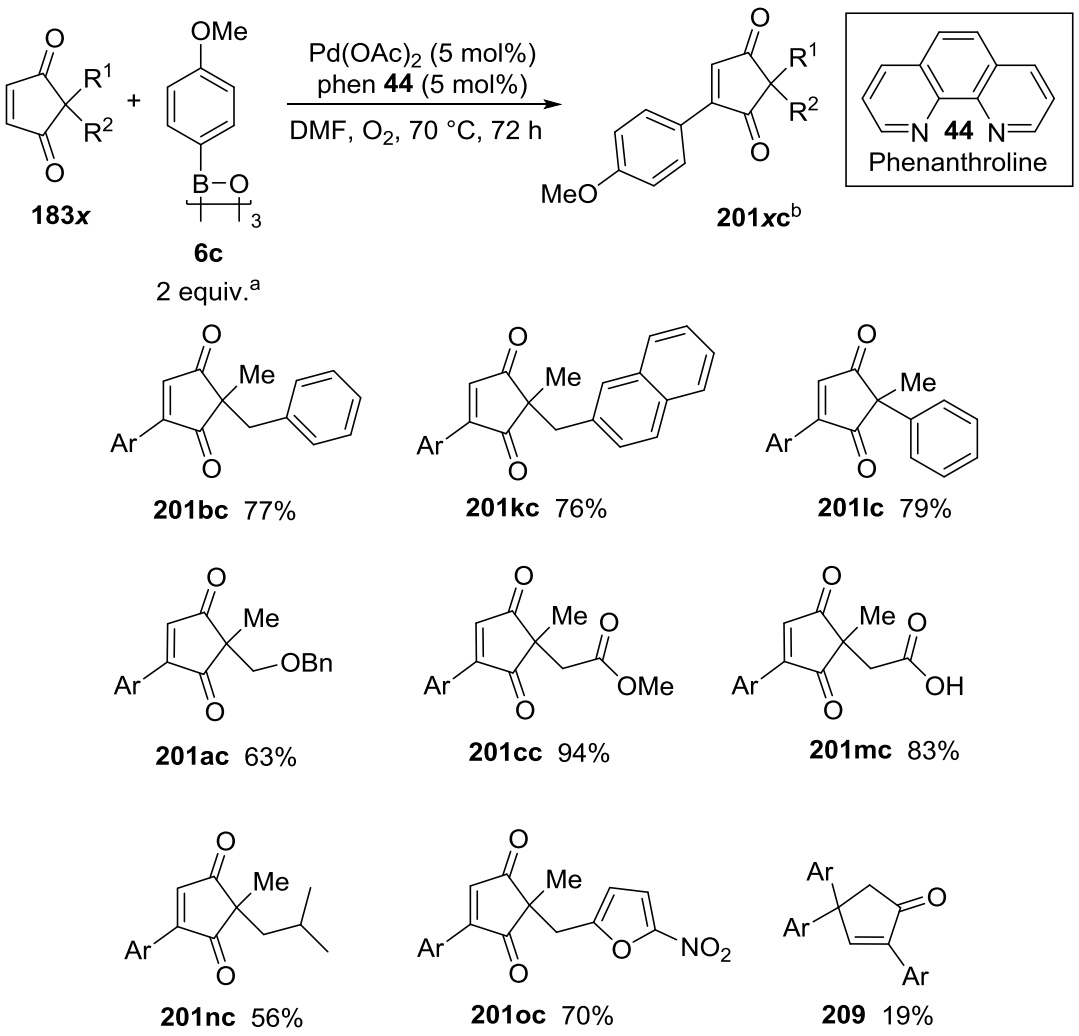
4.3.2 Oxidative Heck reaction – substrate screen

Early work on this project, specifically on the racemic oxidative Heck reaction was carried out in collaboration with MChem and short term undergraduate project students in the Lee Group. After extensive optimisation examining potential Pd(II) catalysts, ligands and temperature, appropriate reaction conditions were obtained. Nitrogen- (as opposed to phosphorus-) based ligands were screened given they have been found to be effective in oxidative Heck reactions and are not prone to oxidation.[26, 27] Palladium(II) acetate was found to be an appropriate palladium source and phenanthroline the most effective ligand for the reaction. DMF (0.1 mM concentration) was used as a solvent with molecular oxygen as the oxidant. Heating the reaction to 70 °C was necessary for good yields. For the substrate scope, it was found that 5 mol% of both catalyst and ligand was sufficient for the reaction to proceed in good yield. Additionally, optimisation studies found that using boroxines as the coupling partner (formed by dehydrating the commercial boronic acid by heating under vacuum) gave higher yields than using the corresponding boronic acid (Scheme 101).



Scheme 101: Optimised reaction conditions for oxidative Heck substrate screen

With the optimised reaction conditions in hand, the substrate screen was performed in collaboration with other Lee group members. An initial substrate screen was carried out by MChem project student Claire Lamb (Scheme 102).



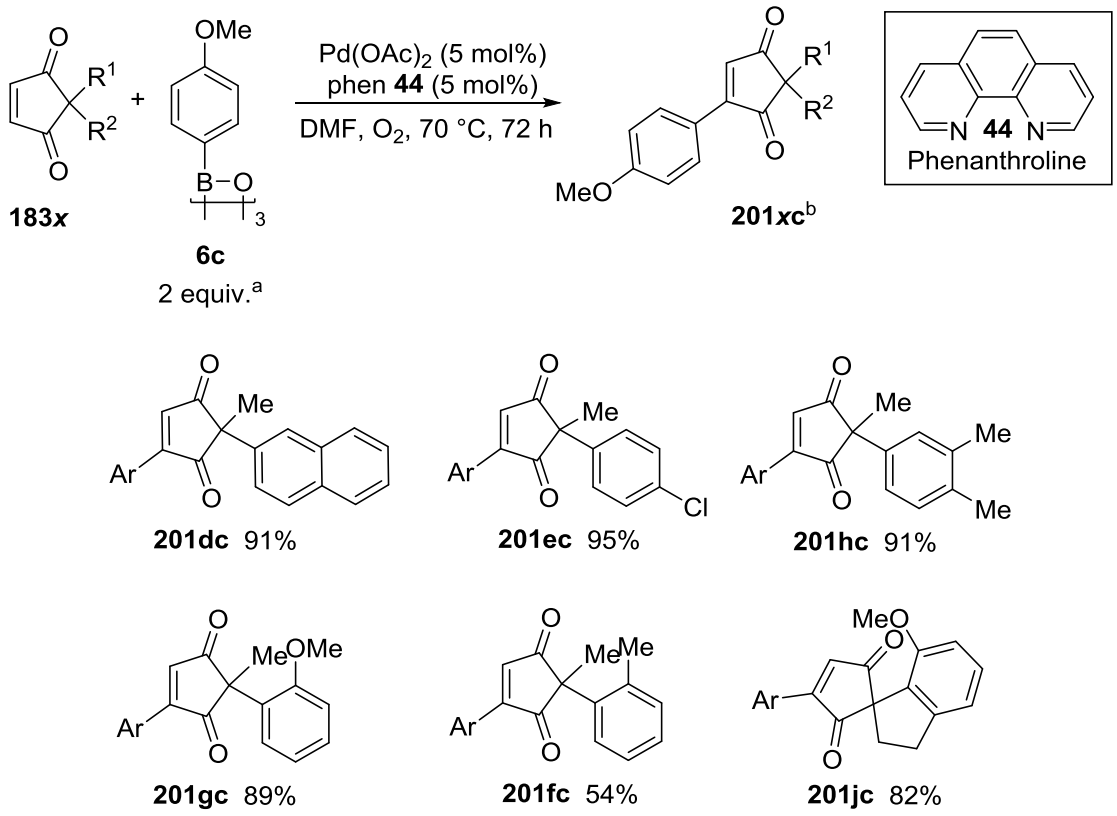
[a]Equivalents of single aryl group of the boroxine trimer. [b]Isolated yields.

Scheme 102: Oxidative Heck reaction of 2,2-disubstituted cyclopentene-1,3-dione substrates and tris(*p*-methoxyphenyl)boroxine

Pleasingly, the substrate screen demonstrated that the reaction conditions are tolerant of a wide variety of substrates with various functional groups of differing steric and electronic properties. Substrates bearing phenyl and benzyl substituents are well tolerated and gave comparable yields (**201bc, 201kc** and **201lc,** 77%, 76% and 79% respectively). Various other functional groups including a protected alcohol (**201ac**, 63%), ester (**201cc**, 94%) and acid (**201mc**, 83%) gave decent to excellent yields and an alkyl group is also tolerated (**201nc**, 56%). Pleasingly, a substrate bearing a heterocycle also gave a good 70% yield (**201oc**). However, unsubstituted cyclopentenedione with

enolisable protons does not give the desired product but instead a trisubstituted enone (**209**), which is possibly formed *via* tautomerisation of the oxidative Heck product followed by 1,2 addition.[28, 29]

Following this substrate screen, we wanted to expand the substrate scope further. The author therefore investigated a number of other substrates to probe how substituents on the aryl ring would affect yield. Additionally, a naphthyl substrate and a spiro compound were added to this screen (Scheme 103).



[a]Equivalents of single aryl group of the boroxine trimer. [b]Isolated yields.

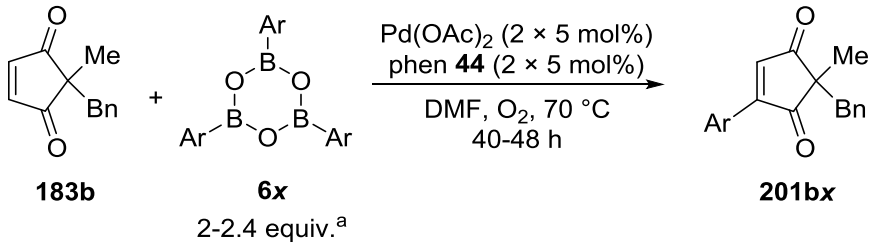
Scheme 103: Additional substrate screen including substrates with substituted aryl groups

Pleasingly, decent to excellent yields were obtained in this additional substrate screen (Scheme 103). Aryl substituents are tolerated and give up to excellent yields whether electron-donating (**201hc, 201gc**) or electron-withdrawing (**201ec**). Whilst an *ortho*-methoxy group was well tolerated (89%, **201gc**), an *ortho*-methyl group did reduce the yield quite considerably (54%, **201fc**). Additionally, substrates bearing a naphthyl substitutent and a spiro centre performed well under the reaction conditions (91%, **201dc** and 82%, **201jc**).

Following on from the successful substrate screen which demonstrated the versatility of the reaction with various functional groups, our attention turned to carrying out a boronic acid screen.

4.3.3 Oxidative Heck reaction – boronic acid screen

The boronic acid screen was conducted in collaboration with undergraduate project students in the Lee Group. Optimisation was carried out using **183b** as the chosen substrate and the reaction conditions used for the substrate screen, were found to be appropriate, with an additional portion of $Pd(OAc)_2$ and 1,10-phenanthroline **44** being added after 24 hours to maximise conversion to product (Scheme 104). A reaction time of 40-48 hours was found to be optimal. The reaction required dry conditions and therefore boronic acids were dehydrated to the corresponding boroxines by heating under vacuum prior to use.

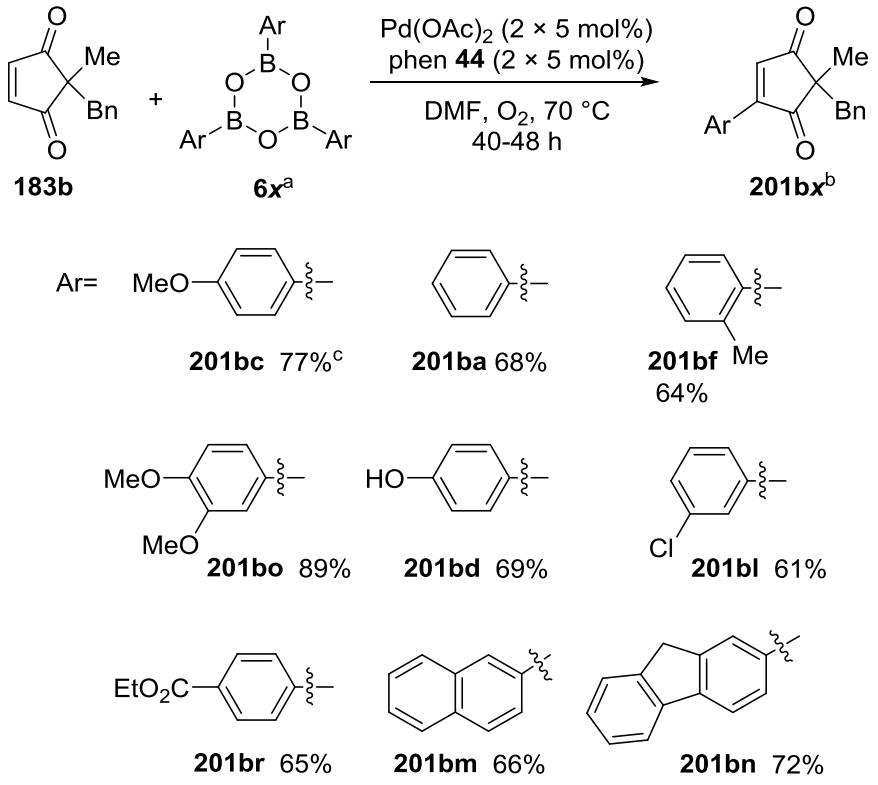


183b **6*x*** 2-2.4 equiv.[a] **201b*x***

[a]Equivalents of single aryl group of the trimer

Scheme 104: Optimised reaction conditions for the boronic acid screen

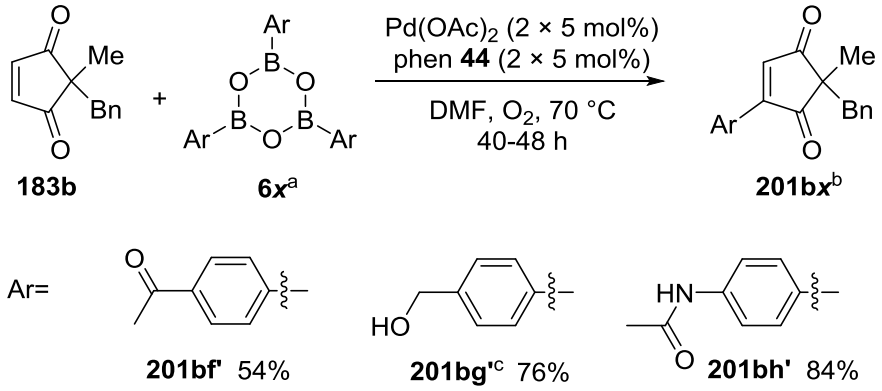
Using the optimised reaction conditions, a range of boronic acids were screened with varying steric and electronic properties and found to give good to excellent yields (Scheme 105). Electron-withdrawing and donating groups (**201bc, 201ba, 201bf, 201bo, 201bd, 201bl** and **201br**), in addition to polyaromatics (**201bm**) are tolerated and give good to very good yields (61-89%). Substituents at various positions on the phenyl ring are tolerated and also provide a potential handle for further functionalisation (for example **201bd, 201bl** and **201br**). Pleasingly, unprotected groups such phenols (**201bd,** 69%) are tolerated as are readily oxidisable groups such as fluorene (**201bn,** 72%).



[a]Commercial arylboronic acid (2 equiv.) is heated under vacuum to generate the arylboroxine prior to use. [b]Isolated yields. [c]Conditions as in Scheme 102.

Scheme 105: Boronic acid screen

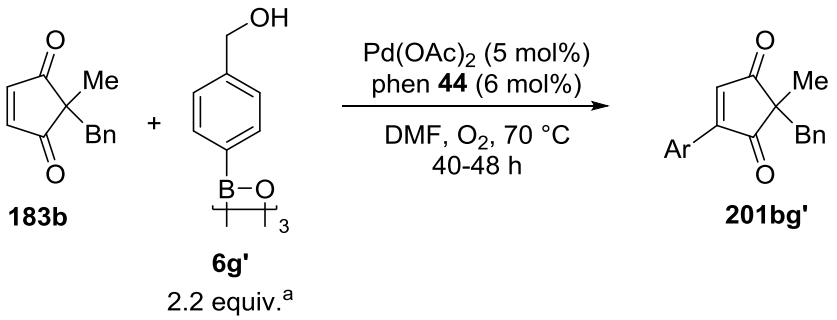
Following on from this boronic acid screen (carried out by MChem project student Claire Lamb), we wanted to further our investigations and demonstrate that the reaction conditions were tolerant of a wider variety of functional groups. The author therefore screened another three boronic acids with ketone, amide and alcohol moieties (Scheme 106).



[a]Commercial arylboronic acid (2 equiv.) is heated under vacuum to generate the arylboroxine prior to use. [b]Isolated yields. [c]$Pd(OAc)_2$ (4 × 5 mol%), phenanthroline (4 × 6 mol%), standard conditions gave a yield of 29% (see Table 24).

Scheme 106: Additional boroxine screen to further investigate functional group tolerance.

Both the ketone and amide boronic acids were well tolerated with moderate to very good yields obtained (54%, **201bf'** and 84%, **201bh'** respectively). However, when using the optimised reaction conditions with 4-hydroxybenzyl boronic acid, the initial yield was very poor (29%, **201bg'**) and further optimisation was deemed necessary (Table 24).



[a]Commercial arylboronic acid is heated under vacuum to generate the arylboroxine prior to use.

Entry	Additional portions of $Pd(OAc)_2$, ligand and boroxine	Reaction time (h)	Yield 201bg' (%)[a]
1	24 h – 5 mol% $Pd(OAc)_2$ and 6 mol% ligand	42	29
2	24 h and 48 h – 5 mol% $Pd(OAc)_2$, 6 mol% ligand and 2.2 equiv. boroxine	96	-
3	24, 28 and 32 h – 5 mol% $Pd(OAc)_2$ and 6 mol% ligand	48	76

[a]Isolated yields.

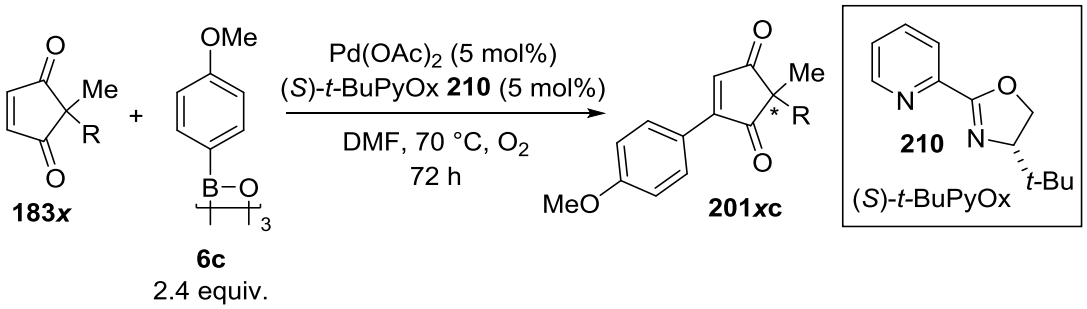
Table 24: Investigating portionwise addition with 4-hydroxybenzyl boronic acid

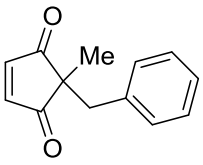
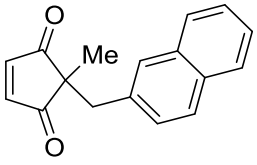
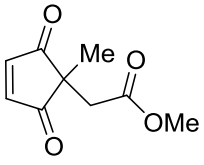
Firstly, additional portions of catalyst, ligand and boronic acid were added to the reaction and the reaction time increased (Table 24, Entry 2). Unfortunately, this did not have the desired effect of increasing the yield and a reduction in yield was actually observed (in fact no product could be isolated) compared to when one portion of catalyst and ligand was used (Entries 1 and 2). A possible reason for this is that the addition of extra boronic acid was rendering the catalyst inactive, possibly due to coordination of the hydroxyl group to palladium. Therefore, we decided to only add additional portions of catalyst and ligand. Increasing the catalyst loading to four portions of ligand and $Pd(OAc)_2$ over a 48 hour period increased the yield of **201bg'** to 76% (Entry 3).

4.4 Oxidative Heck reaction – developing the enantioselective protocol

Following on from the extensive studies into the racemic oxidative Heck reaction between cyclopentene-1,3-diones and aryl boroxines, we turned our attention to investigating the potential of carrying out the reaction enantioselectively.

The conditions chosen for initial studies were those used for the substrate screen, and the commercially available chiral ligand (*S*)-4-*tert*-butyl-2-(2-pyridyl)oxazoline [(*S*)-*t*-BuPyOx] was selected given there are various examples in literature of its use as an effective chiral ligand in Pd(II) catalysis.[14, 30, 31] At this stage our aim was to see if the oxidative Heck reaction could be performed enantioselectively, after which further optimisation studies would be carried out in order to increase both enantiomeric ratio and yield (Table 25).



Entry	Substrate	Yield (%)[a]	Enantiomeric ratio
1	 **183b**	**201bc** 66	76:24
2	 **183k**	**201kc** 29	52:48
3	 **183c**	**201cc** 65	75:25

[a]Isolated yields.

Table 25: Initial studies into the enantioselective oxidative Heck reaction*

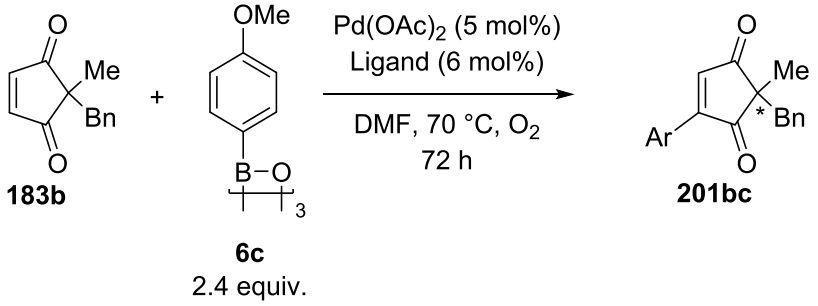
* Initial screen carried out by Claire Lamb, MChem project student.

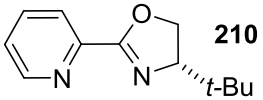
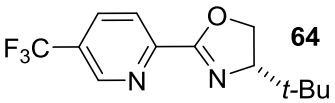
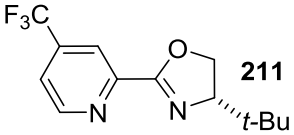
The initial studies carried out by MChem project student Claire Lamb produced some very promising results. Yields were good for substrates **183b** and **183c** (Table 25, Entries 1 and 3), although a considerable drop in yield (and enantiomeric ratio) was observed for more sterically encumbered substrates such as **183k** (Entry 2). More importantly, the enantioselectivity whilst moderate, showed potential with enantiomeric ratios of up to 76:24 (Entry 1).

These results certainly showed promise in terms of developing an enantioselective protocol for this reaction in order to obtain both good yields and enantioselectivity. However, upon further optimisation (see Sections 4.4.1 and 4.4.2), enantioselectivity was poor and unfortunately the initial results shown in Table 25 could not be repeated, requiring extensive further optimisation of the enantioselective protocol.

4.4.1 Enantioselective oxidative Heck reaction – initial ligand screen

Following on from the initial promising results obtained by Claire Lamb using (*S*)-*t*-BuPyOx **210** as the chiral ligand,[32] our aim was to further optimise the reaction conditions in order to increase the enantioselectivity of the reaction. The first variable examined was the choice of ligand. Using the same conditions, we screened an additional two commercially available PyOx ligands with substituents on the pyridinyl ring[33] (Table 26) to investigate if the enantioselectivity could be improved.



Entry	Ligand	Yield 201bc (%)[a]	Enantiomeric ratio
1[b]	 **210**	66	76:24
2	 **64**	46	62:38
3	 **211**	45	61:39

[a] Isolated yields. [b]Initial result by Claire Lamb (MChem project student).

Table 26: Enantioselective oxidative Heck reaction - ligand screen

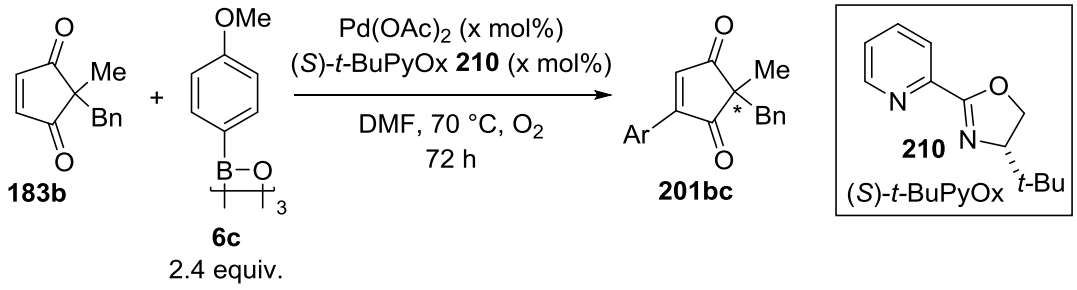
When substituted (*S*)-*t*-BuPyOx ligands **64** and **211** were screened (Table 26, Entries 2 and 3), both the enantioselectivity and the yield dropped considerably compared to our initial promising result with ligand **210** (Entry 1). It was therefore apparent that further, more extensive optimisation studies were necessary in order to increase both the yield and enantiomeric ratio of the desired product.

4.4.2 Enantioselective oxidative Heck reaction – further optimisation

Catalyst loading and premixing of the catalyst

Following on from the aforementioned initial ligand screen (Table 26), further optimisation studies commenced with repeating the best result from the original substrate screen using (*S*)-*t*-BuPyOx **210**, followed by examining whether increasing catalyst loading would have a positive effect on enantiomeric ratio. Given that the priority at this point in the project was to optimise reaction conditions to give a good enantiomeric ratio, chiral HPLC analysis was carried out on the reaction mixture after work up and therefore isolated yields or conversions were not obtained.

We also examined whether premixing of the catalyst [$Pd(OAc)_2$, DMF and ligand] for one hour before adding the substrate and boroxine would be effective in increasing the enantioselectivity (Table 27). This methodology had been employed by Jung and coworkers in their investigations into asymmetric Heck-type reactions and found to increase the enantioselectivity.[34]



Entry	$Pd(OAc)_2$ (mol%)	Ligand (mol%)	Enantiomeric ratio	Comments
1[a]	5	6	76:24	Initial result by Claire Lamb
2	5	6	58:42	
3[b]	5	6	57:43	Ligand, DMF and $Pd(OAc)_2$ stirred at rt for 1 h
4	10	11	57:43	Ligand, DMF and $Pd(OAc)_2$ stirred at rt for 1 h

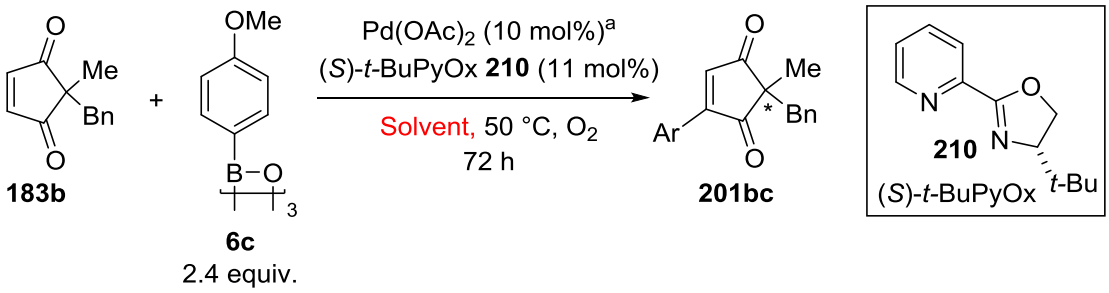
[a]Table 25, Entry 1. [b]Enantiomeric ratio measured every 24 h during reaction and found to remain constant.

Table 27: Catalyst loading optimisation

On repeating the initial promising result obtained by Claire Lamb, unfortunately the enantiomeric excess was not comparable, confirming the need for further extensive optimisation (Table 27, Entries 1 *versus* 2). We examined the effect of premixing $Pd(OAc)_2$, DMF and ligand and found that regardless of catalyst loading, the enantioselectivity did not change (Entries 3 and 4). We also examined whether the enantiomeric excess varied during the course of the reaction in order to investigate whether reaction time affected enantioselectivity in addition to yield. By analysing aliquots of reaction mixture (Entry 4) at 24 hour intervals the enantiomeric excess was found to remain constant throughout the reaction.

Solvent screen

Our attention next turned to carrying out a small solvent screen. Using 10 mol% catalyst and 11 mol% (S)-*t*-BuPyOx **210** as the chiral ligand, a number of different solvents were investigated, which were less ligating than DMF, in the hope of boosting enantioselectivity.[35] In previous work by Jung and co-workers on asymmetric Heck-type couplings it was hypothesised that moderate enantioselectivities were due to background reactions facilitated by the free palladium catalyst rather than the ligand-chelated catalyst.[34] In the same study, Jung and co-workers found that premixing the ligand and catalyst prior to adding the reagents increased enantioselectivity (*vide supra*), in addition to using a premade catalyst (which will be discussed in the following section). Therefore, the ligand, $Pd(OAc)_2$ and solvent were premixed for one hour at room temperature before the substrate and boroxine were added. Additionally, the reaction temperature was lowered to 50 °C to examine the effect on enantioselectivity.



Entry	Solvent	Enantiomeric ratio
1	DMF	59:41
2	$CHCl_3$	No product formed
3	DMA	65:35

[a]Ligand, solvent, $Pd(OAc)_2$ stirred at rt for 1 h prior to adding substrate and boroxine.

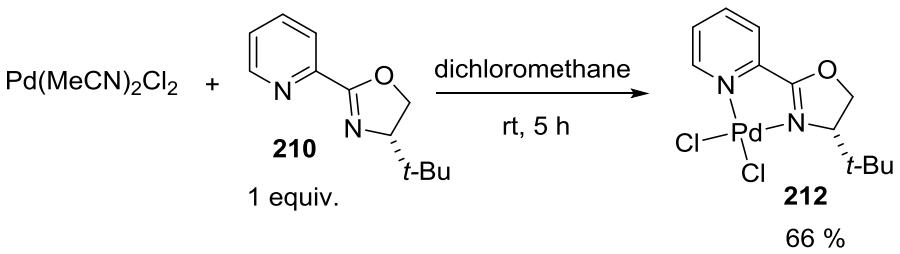
Table 28: Solvent screen

Unfortunately the reaction using chloroform as the solvent did not yield product (Table 28, Entry 2). However, a slight increase in enantioselectivity was observed when DMA was used as the solvent (Entry 3).

Studies into preforming the catalyst

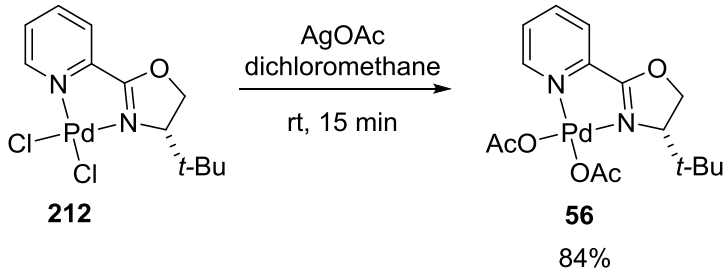
Next our attention turned to investigating whether preforming and isolating the catalyst rather than forming it *in situ* would improve enantioselectivity.

The catalyst was synthesised according to a known literature method used by Jung and co-workers in their studies into asymmetric Heck-type reactions using Pd(II) (Scheme 107).[34]



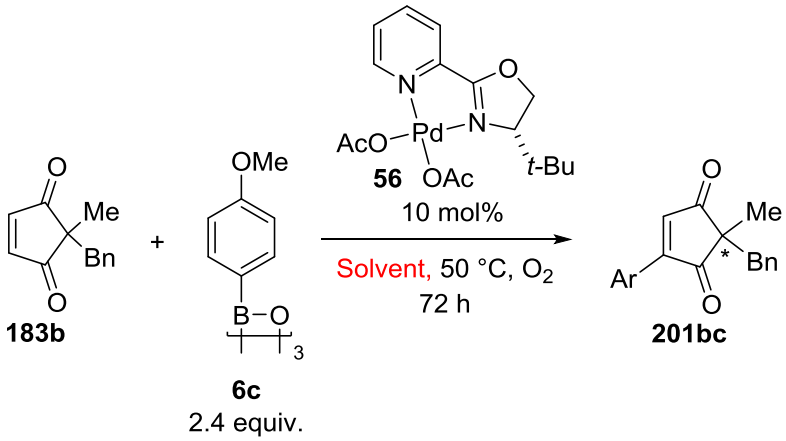
Scheme 107: Synthesis of catalyst precursor **212**

Synthesis of the catalyst precursor gave a reasonable yield of **212** (Scheme 107). Reacting this precursor with silver acetate formed the desired catalyst **56** in good yield (Scheme 108).



Scheme 108: Synthesis of catalyst **56**

The premade catalyst **56** (10 mol%) was used in two reactions conducted at 50 °C using DMF and DMA as solvents (Table 29).



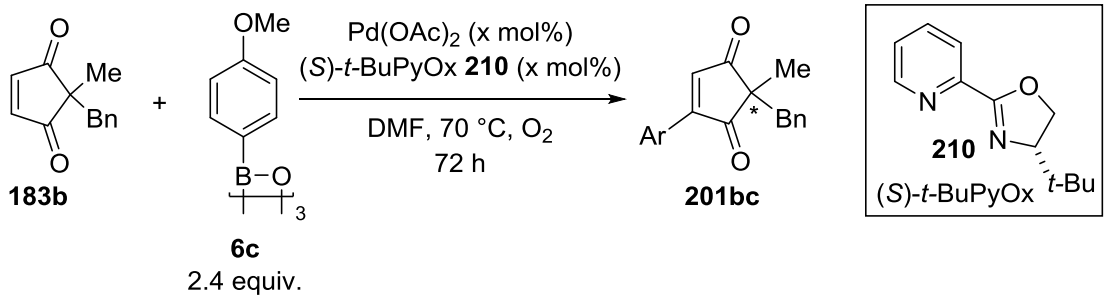
Entry	Solvent	Enantiomeric ratio
1	DMF	59:41
2	DMA	65:35

Table 29: Solvent screen using premade catalyst

Whilst the premade catalyst **56** was effective in inducing some degree of enantioselectivity, there was no change in the enantioselectivity compared to when 10 mol% $Pd(OAc)_2$ and 11 mol% ligand were added separately to the reaction (Table 28, Entries 1 and 3). Given potential stability issues with the premade catalyst and to simplify the reaction procedure, it was decided to continue optimisation studies using the *in situ* generated catalyst [$Pd(OAc)_2$ and (*S*)-*t*-BuPyOx **210**].

Investigations into possible background reactions

Given the enantiomeric ratios to date were very poor, it was worth investigating if any background reaction was taking place in the absence of ligand. We therefore took the original conditions using DMF as a solvent, a temperature of 70 °C and 5 mol% $Pd(OAc)_2$ in the absence of ligand to investigate if the reaction would still proceed.



Entry	mol% $Pd(OAc)_2$	mol% ligand 210	Enantiomeric ratio
1[a]	5	6	58:42
2	5	0	Trace product, 91% starting material isolated

[a]Table 27, Entry 2.

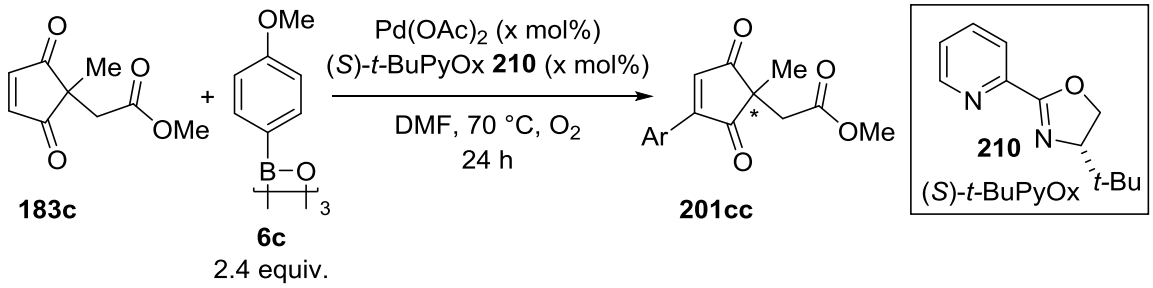
Table 30: Reactions with and in the absence of ligand

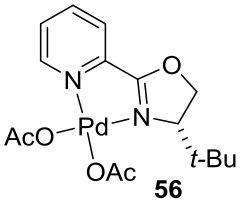
Trace product was obtained from the reaction carried out in the absence of ligand (Table 30, Entry 2). Given that starting material was isolated, we can therefore assume that limited background reactions are occurring which would potentially be eroding the enantiomeric ratio.

Optimisation using methyl 2-(1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate as the substrate

Given that optimisation studies using the benzyl substituted substrate **183b** were not showing any significant improvement in enantioselectivity, we decided to investigate using a different substrate.

Initial studies (Table 25) had shown that substrate **183c** bearing an ester substituent could be used in the enantioselective reaction to give an enantiomeric ratio of 75:25 and therefore we decided that it would be worth investigating if this result could be optimised further (Table 31).



Entry	$Pd(OAc)_2$ (mol%)	Ligand 210 (mol%)	Enantiomeric ratio	Notes
1[a]	5	5	75:25	Initial result by Claire Lamb (Table 25, Entry 3)
2[b]	5 mol% premade catalyst  **56**	-	Trace product	
3	5	6	47:53	

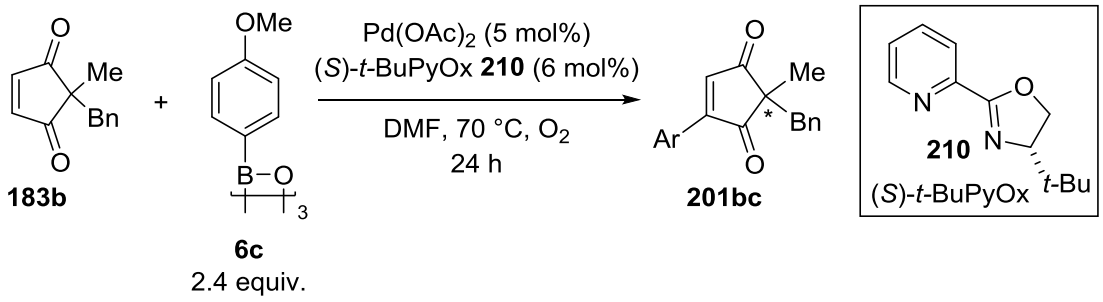
[a]72 h, Table 25, Entry 3. [b]Reaction monitored and starting material present after 24 and 48 h.

Table 31: Optimisation with methyl 2-(1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate as the substrate

Using DMF as the solvent for ease of comparison with previous results and a temperature of 70 °C, two reactions were carried out using both the premade catalyst **56** and repeating the original result using this substrate **183c** (Table 31). Unfortunately, the reaction using the premade catalyst did not yield product (Entry 2). Repeating the initial promising result using 5 mol% $Pd(OAc)_2$ and 6 mol% (*S*)-*t*-BuPyOx **210** the enantioselectivity was not comparable, with a poor enantiomeric ratio of 47:53 (Entry 3 cf. Entry 1). Given these results, we returned to using the original substrate **183b** bearing a benzyl substituent to continue optimisation studies.

Investigating boronic acid sources

In other investigations in the Lee Group, the source of boronic acid has had an impact on results and we therefore screened boronic acids from both Sigma Aldrich and Fluorochem to probe whether the commercial source would affect results (Table 32).



Entry	Boronic acid source	Boronic acid or boroxine	Enantiomeric ratio
1[a]	Sigma Aldrich	Boronic acid from bottle dehydrated to boroxine	58:42
2	Sigma Aldrich	Boronic acid from bottle recrystallised then dehydrated to boroxine	57:43
3	Sigma Aldrich	Directly used from bottle – no dehydration	57:43
4	Fluorochem	Boronic acid from bottle dehydrated to boroxine	56:44

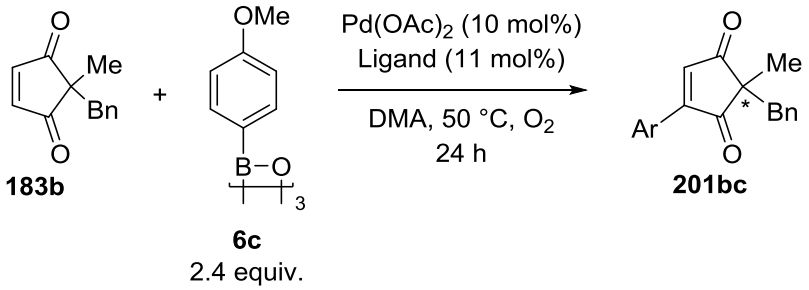
[a]72 h, Table 27, Entry 2.

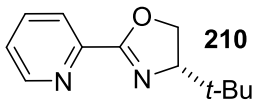
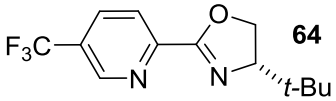
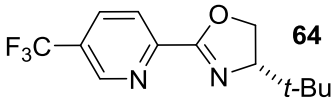
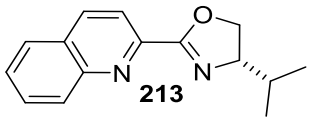
Table 32: Investigating affect of boronic acid source on enantioselectivity

This screen demonstrated that in this case (and as should be expected), the source of boronic acid did not affect the enantioselectivity of the reaction. Using the boroxine generated either from the commercial boronic acid (Table 32, Entry 1), or the commercial boronic acid which was then recrystallised and dehydrated (Entry 2), did not have any effect on the enantiomeric ratio. Additionally, using the commercial boronic acid rather than dehydrating to the boroxine did not have an effect on enantioselectivity of the reaction (Entry 3). Our studies also showed that the source of boronic acid did not affect enantioselectivity (Entries 1 and 4).

Ligand screen using premixed catalyst

Next, we decided to investigate how premixing of the catalyst would affect the enantioselectivity of the reaction. The highest enantiomeric ratio obtained up to this stage in our optimisation studies was using (S)-*t*-BuPyOx **210** as the ligand and premixing this with DMA and $Pd(OAc)_2$ prior to adding the substrate and boroxine (Table 28, Entry 3). We therefore applied these conditions to a couple of reactions using different ligands (Table 33, Entries 2 and 4). Additionally, premixing of the catalyst had been carried out at room temperature and therefore we also investigated whether raising the temperature to 50 °C would have an effect on enantioselectivity (Entry 3 cf. Entry 2).



Entry	Ligand	Conditions	Enantiomeric ratio
1[a]	 **210**	Premixing solvent, ligand and catalyst for 1 h at rt	65:35
2	 **64**	Premixing solvent, ligand and catalyst for 1 h at rt	64:36
3	 **64**	Premixing solvent, ligand and catalyst for 1 h at 50 °C	65:35
4	 **213**	Premixing solvent, ligand and catalyst for 1 h at rt	Racemic

[a]72 h, Table 28, Entry 3.

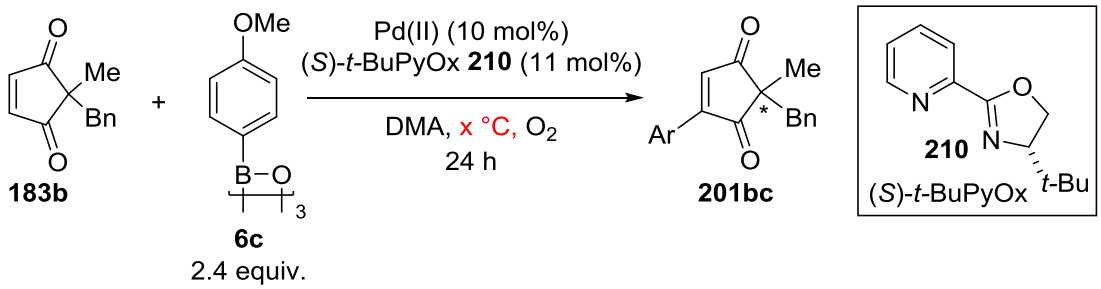
Table 33: Ligand screen using a premixed catalyst and dimethyl acetamide as solvent

Our results showed that the temperature at which the catalyst was premixed prior to adding substrate and boroxine did not affect enantioselectivity (Table 33, Entries 2 and

3). Additionally, no change in enantioselectivity was observed when ligand **64** was used compared to the unsubstituted ligand **210** (Entry 2 cf. Entry 1). However, when the quinoline based ligand **213** was employed, no enantioselectivity was observed (Entry 4). Given that (*S*)-*t*-BuPyOx **210** is cheaper than ligand **64**, and that they both induce the same level of enantioselectivity, we used the unsubstituted ligand **210** and the conditions shown in Entry 1 for further optimisation studies into whether changing the palladium source would affect enantioselectivity.

Investigating the effect of palladium source on enantioselectivity

Optimisation studies to date had used palladium(II) acetate as the palladium source and we therefore decided to investigate whether using the more cationic $Pd(OCOCF_3)_2$ in DMA would affect enantioselectivity (Table 34).



Entry	Catalyst	Temperature	Enantiomeric Ratio
1[a]	$Pd(OAc)_2$	50 °C	65:35
2	$Pd(OAc)_2$	25 °C	69:31
3	$Pd(OCOCF_3)_2$	50 °C	66:34

[a]Table 28, Entry 3.

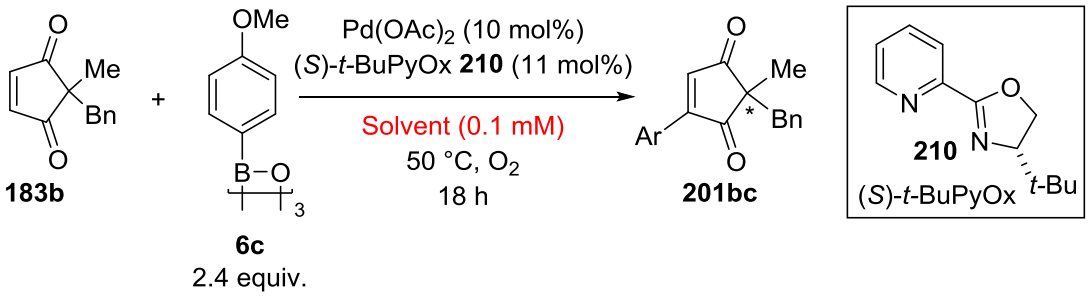
Table 34: Effect of changing the palladium source and temperature on enantioselectivity

On using $Pd(OCOCF_3)_2$ as opposed to $Pd(OAc)_2$ as the palladium source, the enantioselectivity did not change (Table 34, Entry 1 compared to Entry 3). Additionally, as part of this study we also investigated whether lowering the reaction temperature to 25 °C affected enantioselectivity. Whilst the enantioselectivity did increase when a lower temperature was used (69:31, Entry 2 compared to 65:35, Entry 1), the conversion was very poor (~11%) in comparison to using a reaction temperature of 50 °C (40%). Conversions were calculated by integrating the starting material and

product peaks in HPLC traces for each reaction. Therefore, we decided that in order to obtain good yields, the higher temperature would be more favourable for future reactions. Also given that changing the palladium source did not appear to significantly increase enantioselectivity, we also decided to continue to use $Pd(OAc)_2$ as the catalyst.

Extensive solvent screen

Given that the enantioselectivities obtained in optimisation studies still remained moderate, a more extensive solvent screen was carried out to investigate whether the enantiomeric ratio of the reaction could be improved. We screened a number of aprotic solvents with varying polarities (Table 35). Substrate **183b** and tris(*p*-methoxyphenyl)boroxine **6c** were used with a catalyst loading of 10 mol% $Pd(OAc)_2$ and 11 mol% (*S*)-*t*-BuPyOx **210**.



Entry	Solvent	Enantiomeric ratio
1	Acetonitrile	70:30
2[a]	Dimethyl carbonate	48:52
3	Acetone	66:34
4	NMP (1-methyl-2-pyrrolidinone)	63:37
5	Dioxane	Racemic
6	Tetramethyl urea	55:45

[a]Complex mix of products including oxidative Heck product.

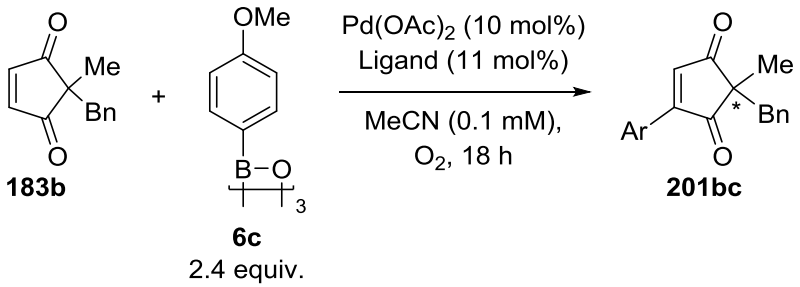
Table 35: Solvent screen

The results obtained showed a varying degree of enantioselectivity depending on the solvent used. Non polar dioxane gave a racemic product (Table 35, Entry 5), as did dimethyl carbonate (Entry 2). The use of tetramethyl urea also induced poor enantioselectivity (Entry 6). However, acetone and NMP (66:34 and 63:37 er respectively, Entries 3 and 4) performed better and pleasingly when acetonitrile was

used as a solvent the enantiomeric ratio increased to 70:30. Being the best result to date and an improvement on the enantiomeric ratio when DMA was used as a solvent (65:35 er, Table 28, Entry 3), it was decided to further investigate using acetonitrile as the solvent.

Temperature and ligand screen using acetonitrile as the solvent

Following on from the promising result obtained when acetonitrile was used as the solvent (Table 35, Entry 1), our optimisation work turned to screening various ligands and reaction temperatures to see if the enantioselectivity could be improved upon. Substrate **183b** and tris(*p*-methoxyphenyl)boroxine **6c** were used, with a catalyst and ligand loading of 10 mol% and 11 mol% respectively (Table 36).



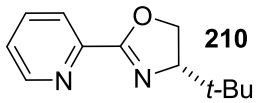
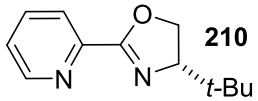
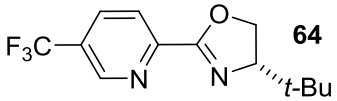
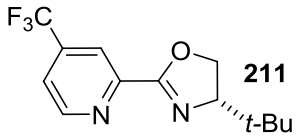
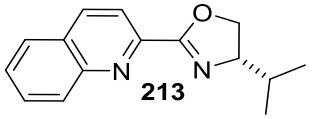
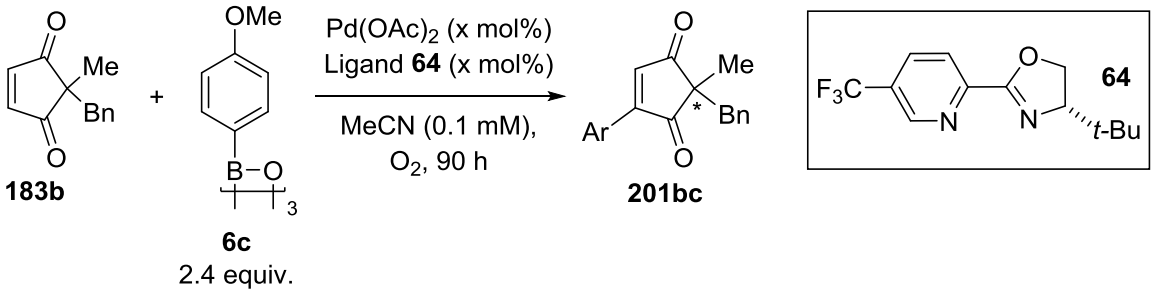
Entry	Ligand	Temp.	Enantiomeric ratio
1	 **210** *t*-Bu	20 °C	78:22
2	 **210** *t*-Bu	35 °C	73:27
3	 **64** *t*-Bu	20 °C	83:17
4	 **211** *t*-Bu	20 °C	83:17
5	 **213**	20 °C	No reaction

Table 36: Ligand and temperature screen with acetonitrile as solvent

Using (*S*)-*t*-BuPyOx **210** as the ligand, two reactions were carried out at 20 and 30 °C, and an increase in enantioselectivity was observed compared to when a reaction temperature of 50 °C was used (70:30 er, Table 35, Entry 1 compared to Table 36, Entries 1 and 2). As expected, an increase in enantioselectivity was observed at lower temperatures. Given this result, a number of other ligands were also screened at 20 °C and enantioselectivity increased to 83:17 er using substituted (*S*)-*t*-BuPyOx ligands (**64** and **211**, Entries 3 and 4). However, no conversion to oxidative Heck product was observed when ligand **213** bearing a quinoline moiety was used (Entry 5).

Investigating yield using acetonitrile as the solvent

From our investigations into ligand and temperature using acetonitrile as the chosen solvent, it was clear from TLC analysis and presence of starting material in HPLC analysis, that conversions were poor. Therefore, attention turned to increasing conversion to oxidative Heck product. Catalyst loading and temperature were investigated and conversions determined (Table 37).



Entry	$Pd(OAc)_2$ (mol%)	Ligand 64 (mol%)	Temp.	Yield
1	3 × 5 mol% added at 0, 24 and 48 h	3 × 6 mol% added at 0, 24 and 48 h	20 °C	95% starting material recovered
2	20	25	35 °C	90% starting material recovered
3	20	25	50 °C	68% starting material recovered, complex mixture of other products
4	20	25 + 1 equiv. benzoquinone	50 °C	No reaction[a]

[a]No product visible by ^{1}H NMR or TLC analysis.

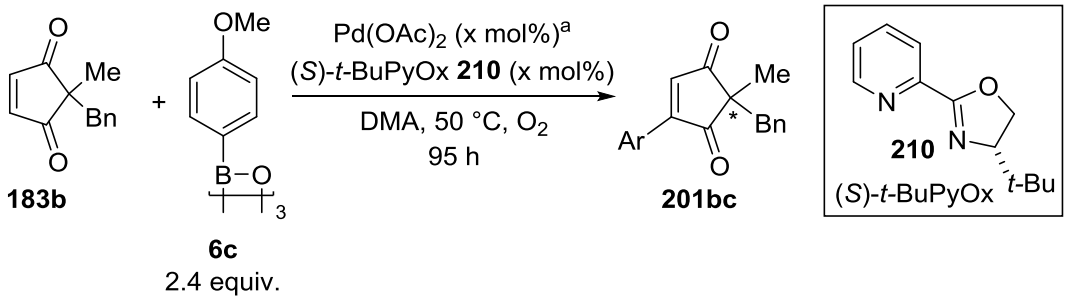
Table 37: Investigating catalyst loading and temperature with acetonitrile as solvent

Unfortunately in all the reactions carried out, regardless of catalyst loading, only trace product was formed and a considerable amount of starting material (Table 37, Entries 1 and 2), in addition to a complex mixture of other products (Entry 3) was evident from purification of the reactions by column chromatography. Given the very poor conversions, another reaction was carried out using one equivalent of benzoquinone as an additional oxidant to probe whether molecular oxygen was perhaps being ineffective in reoxidising the catalyst. However, no reaction occurred (Entry 4).

Despite the promising enantioselectivity in the reactions carried out in acetonitrile, the very poor conversions indicated that this would not be a viable solvent to use in future studies. Therefore our investigations returned to using dimethyl acetamide as the reaction solvent which had given the most promising enantioselectivity and reasonable conversions.

Ligand loading studies using dimethyl acetamide as solvent

The majority of optimisation studies had solely focused on examining enantiomeric ratio rather than yield. Although TLC and HPLC analysis had indicated that conversions to product when DMA was used as the solvent were reasonable compared to acetonitrile, it was obviously prudent to investigate this further. We repeated one of our earlier optimisation reactions (Table 28, Entry 3) in order to isolate the product and obtain a yield. A reaction time of four days was chosen in order to maximise conversion of starting material to product. Additionally, another reaction was carried out using double the ligand loading (20 mol%) in order to investigate if this would affect yield or enantioselectivity (Table 38).



Entry	$Pd(OAc)_2$ (mol%)	Ligand 210 (mol%)	Enantiomeric ratio	Yield (%)[b]
1	10	11	65:35	81
2	10	20	63:37	82

[a]Ligand, solvent and catalyst premixed for 1 h at rt. [b]Isolated yields.

Table 38: Catalyst loading studies using DMA as solvent

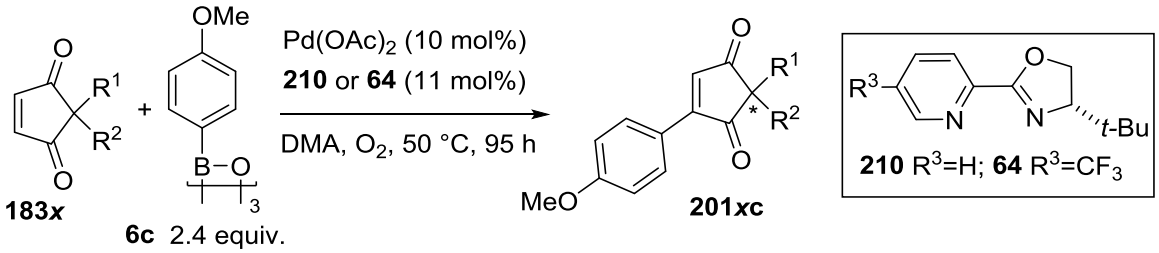
Pleasingly the yield of oxidative Heck product **201bc** was very good and no change (within error) was observed in yield or enantiomeric ratio when a higher ligand loading was used (Table 38, Entries 1 and 2).

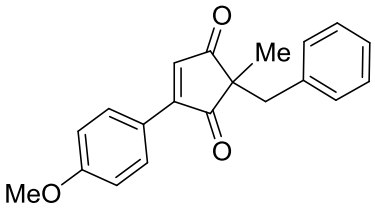
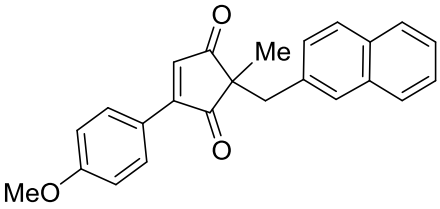
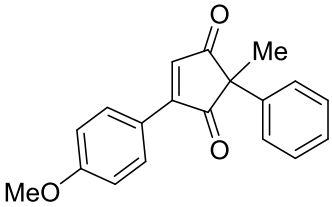
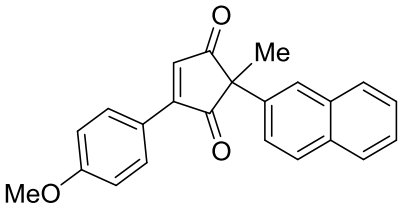
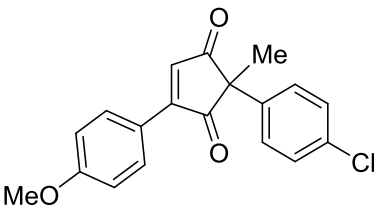
Given the good yield obtained using DMA as the solvent and a catalyst and ligand loading of 10 and 11 mol% respectively (Entry 1), it was decided to take these conditions forward and complete a substrate and boronic acid screen.

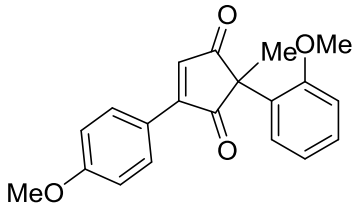
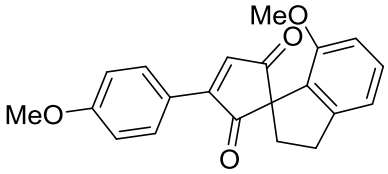
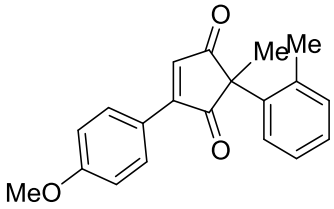
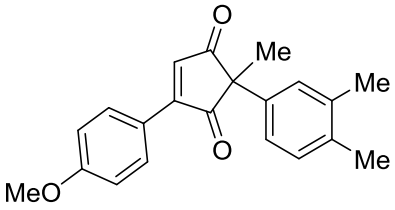
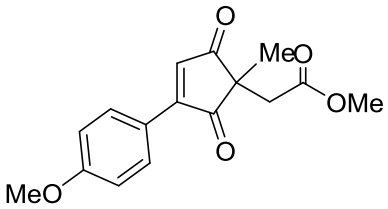
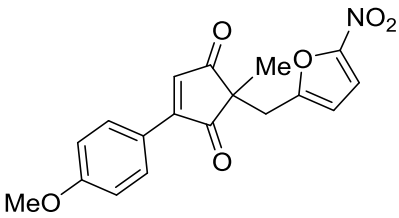
4.4.3 Enantioselective oxidative Heck reaction – substrate screen

Given that our optimisation work had investigated a wide variety of variables and enantioselectivities remained moderate, we decided to continue work on this project by screening a range of substrates in the hope that increased enantioselectivity may be observed. The conditions used in Table 38, Entry 1 were chosen for the screen given the reasonable enantioselectivity and good yield obtained (10 mol% $Pd(OAc)_2$, 11 mol% (*S*)-*t*-BuPyOx **210**, DMA, 50 °C, 95 h). Premixing of the solvent, ligand and $Pd(OAc)_2$ was also carried out prior to adding the substrate and boroxine (Table 39).

Pleasingly, good enantioselectivities were obtained with a number of substrates. Given that ligand screens during initial optimisation work had shown only moderate enantioselectivities (Table 33), any significant difference in ligands was not evident from small changes in enantiomeric ratio. Therefore we decided that it would be worth rescreening a small selection of substrates which gave good enantioselectivity using (*S*)-*t*-BuPyOx **210** in this substrate screen, with ligand (*S*)-4-(*tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** in order to investigate if the now higher enantioselectivities could be improved further by slight changes to the ligand. These results are also included in Table 39, in addition to yields from the racemic reactions carried out with these substrates for comparison purposes.



Entry	Product 201*x*c	Racemic reaction yield[a,b]	Yield[b] and er with 210	Yield[b] and er with 64
1	 **201bc**	79%	81% 65:35	57% 61:39
2	 **201kc**	76%	71% 62:38	
3	 **201lc**	79%	93% 83:17	91% 83:17
4	 **201dc**	91%	99% 90:10	Quant. yield 90:10
5	 **201ec**	95%	98% 78:22	90% 80:20

6	 **201gc**	89%	85% 78:22	Purification not possible[c] 72:28
7	 **201jc**	82%	85% 55:45	
8	 **201fc**	54%	Purification not possible[d] 61:39	
9	 **201hc**	91%	Quant. yield 80:20	99% 80:20
10	 **201cc**	94%	NY[e]	
11	 **201oc**	70%	NY[e]	

Ligand, solvent and catalyst premixed for 1 h at rt. [a]See Scheme 102 for reaction conditions. [b]Isolated yields.
[c]Coelution with starting material. [d]Coelution with phenol. [e]Very poor conversion, no product isolated.

Table 39: Enantioselective oxidative Heck reaction substrate screen

A range of substrates were screened bearing aryl, polyaromatic and heterocylic groups. Enantioselectivity varied depending on the substrate and an increase in enantioselectivity was observed with substrates bearing aryl substituents, as opposed to benzyl groups (Table 39, Entries 3 and 4 cf. Entries 1 and 2) with up to 90:10 enantiomeric ratio obtained (Entry 4). Substrates bearing aryl groups with a range of electron-donating and withdrawing substituents all gave decent enantioselectivities (Entries 5, 6, 8 and 9). However, a substrate bearing a spiro centre induced very little enantioselectivity (55:45 er, Entry 7).

Using the substituted PyOx ligand **64** for selected substrates had various effects depending on the substrate. A very slight increase in the enantiomeric ratio was observed for product **201ec** (Entry 5). The enantioselectivity remained unchanged for some substrates (Entries 3, 4 and 9) and a slight decrease was observed for products **201bc** and **201gc** (Entries 1 and 6).

When substrate **183g** was screened with the two different ligands (Entry 6), conversion reduced upon using the substituted PyOx ligand **64** as coelution of the product with starting material upon purification by column chromatography was observed and thus an isolated yield could not be obtained. This problem was not encountered when ligand **210** was used.

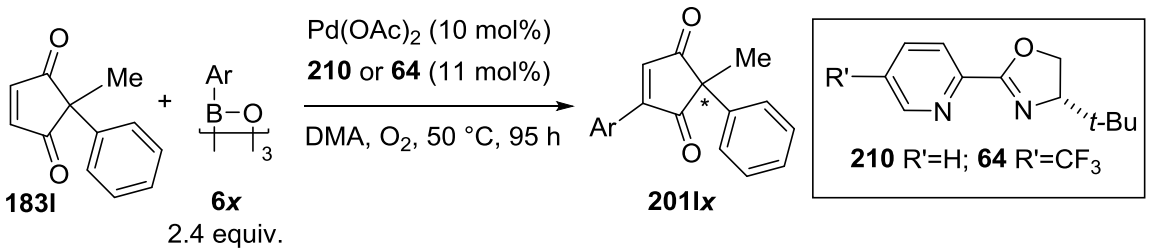
Additionally, unfortunately a yield could not be obtained when substrate **183f** was screened, again for purification reasons. Coelution with an impurity, possibly the phenol of the boronic acid was observed and thus the product **201fc** could not be isolated (Entry 8).

Regrettably, when substrates bearing ester and heterocyclic groups were screened, considerable amounts of starting material were evident and no product could be isolated from the reaction mixture (**201cc** and **201oc**, Entries 10 and 11).

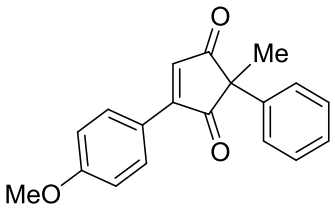
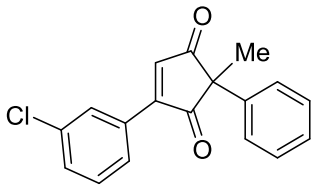
Comparing the yields of the enantioselective reactions to those carried out racemically, yields were generally slightly better or comparable, with a few exceptions where conversions were poorer or where isolation of the product was not possible (Entries 6, 8, 10 and 11).

4.4.4 Enantioselective oxidative Heck reaction – boroxine screen

Next, two different substrates were chosen for the boroxine screen. Firstly, substrate **183l** bearing a phenyl substituent was reacted with tris(*m*-chlorophenyl)boroxine **6l** to investigate whether the enantiomeric ratio would be affected by the electronics of the boronic acid (Table 40). An additional portion of catalyst and ligand was added after one day in order to maximise yield (in line with the boroxine screen conditions for the racemic reaction).



183l **6*x*** 2.4 equiv. **201l*x***

Entry	Product	Racemic reaction yield[a]	Yield[b] and er with 210	Yield[b] and er with 64
1[c]	 **201lc**	79%	93% 83:17	91% 83:17
2	 **201ll**	71%[d]	49%[d] 56:44	

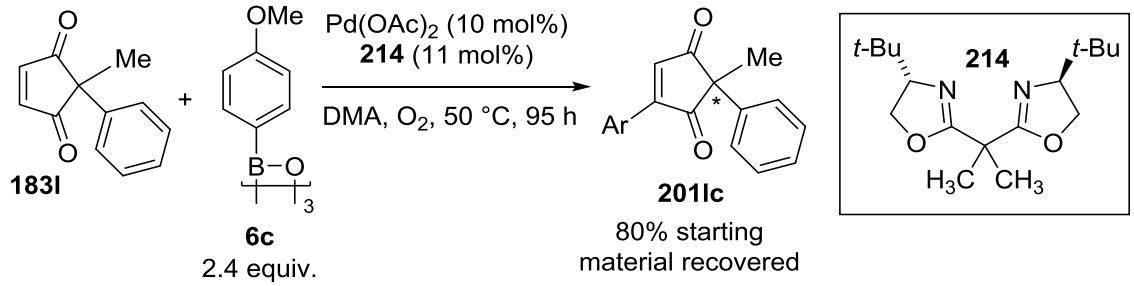
Ligand, solvent and catalyst premixed for 1 h at rt. [a]See Scheme 102 for reaction conditions. [b]Isolated yield. [c]Table 39, Entry 3. [d]Additional 5 mol% $Pd(OAc)_2$ and ligand added after 24 h.

Table 40: Enantioselective oxidative Heck reaction boroxine screen using substrate **183l**

Regrettably, a decrease in enantioselectivity to 56:44 (Table 40, Entry 2) was observed compared to the reaction using tris(*p*-methoxyphenyl)boroxine (83:17 er, Entry 1). Given this result, it was decided to continue with the boroxine screen using substrate

183d which had given the highest enantiomeric ratio in the initial substrate screen (90:10 er, Table 39, Entry 4).

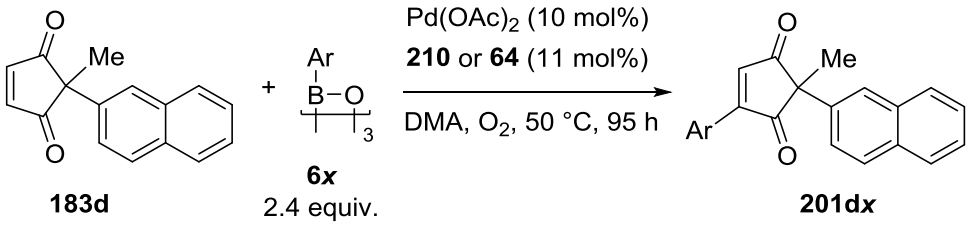
An additional part of the screen shown in Table 40 was to carry out a reaction using substrate **183l** and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] **214** as a ligand. Whilst BOX ligands such as **214** have been employed in enantioselective oxidative Heck studies reported in the literature,[34, 36] early optimisation work had indicated that it was not suitable for this work. We thought it prudent to confirm this before proceeding further using PyOx ligands. Our result confirmed that our choice of ligand was the best for these studies as 80% starting material was recovered from the reaction (Scheme 109).

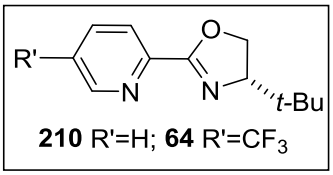


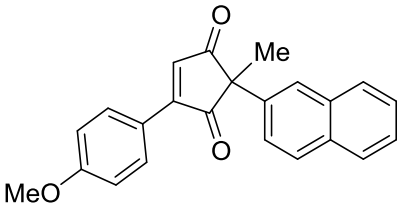
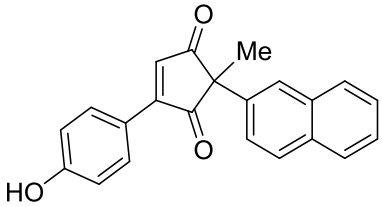
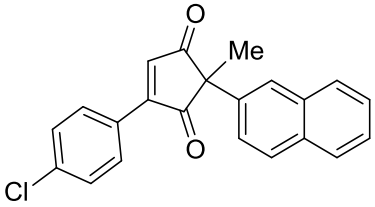
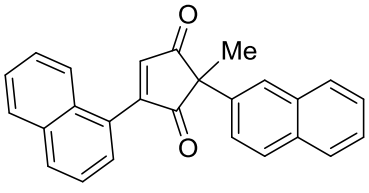
183l **6c** 2.4 equiv. **201lc** 80% starting material recovered

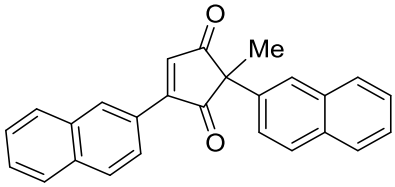
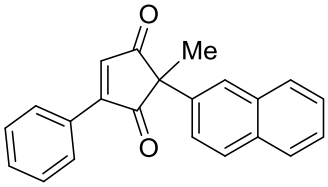
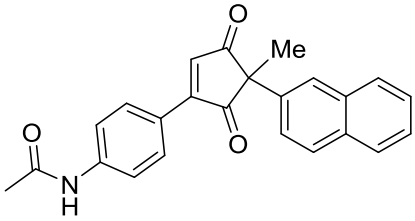
Scheme 109: Enantioselective oxidative Heck reaction using 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] as a ligand

Next, substrate **183d** was screened with a number of boroxines with various steric and electronic properties (Table 41). Racemic reactions were also carried out in order to obtain HPLC separation conditions. These results are also included in the table for comparison of yields. With the exception of 2 results (Entries 4 and 7), yields from the enantioselective reactions were higher in comparison to when the racemic conditions were used.





Entry	Product	Racemic reaction yield[a]	Yield[b] and er with 210	Yield[b] and er with 64
1[c]	 **201dc**	91%	99% 90:10	Quant. yield 90:10
2	 **201dd**	87%[d]	Quant. yield 79:21	Quant. yield 83:17
3	 **201di'**	79%	69% 76:23	85% 94:6
4	 **201dj'**	Purification not possible[e]	Purification not possible[e]	

5	 **201dm**	83%	92% 74:26	
6	 **201da**	84%[f]	97% 74:26	Quant. yield 73:27
7	 **201dh'**	85%[g]		28%[h] 80:20

Ligand, solvent and catalyst premixed for 1 h at rt. [a]See Scheme 102 for reaction conditions. [b]Isolated yields. [c]Table 39, Entry 4. [d]Additional 5 mol% $Pd(OAc)_2$ and ligand added after 24 h. [e]Coelution with phenol. [f]Yield 78% using phenyl boronic acid pinacol ester. [g]Additional 5 mol% $Pd(OAc)_2$ and ligand added after 24 h, reaction left for 48 h. [h]Additional 10 mol% $Pd(OAc)_2$ and ligand added after 48 h.

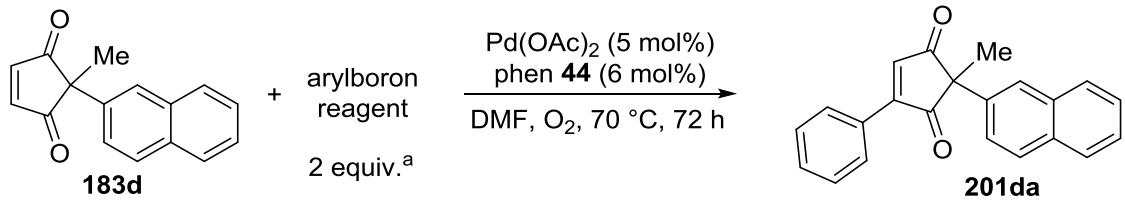
Table 41: Enantioselective oxidative Heck reaction boroxine screen using substrate **183d**

Enantioselectivities from the boroxine screen were very promising with enantiomeric ratios of up to 94:6 achieved when tris(*p*-chlorophenyl) boroxine **6i'** was used with ligand **64** (Table 41, Entry 3). This was a significant improvement to an enantiomeric ratio of 76:23 which was obtained when the unsubstituted PyOx ligand **210** was used with the same substrate and boroxine combination. Aside from this very good result, various other boroxines with differing steric and electronic properties were well tolerated by the reaction conditions. Promising enantioselectivities were obtained ranging from a moderate enantiomeric ratio of 73:27 (but in excellent quantitative yield) when trisphenyl boroxine was used (Entry 6) to 90:10 using tris(*p*-methoxyphenyl) boroxine (Entry 1). Unprotected phenols (Entry 2) and amides (Entry 7) were well tolerated and gave good enantiomeric ratios of 83:17 and 80:20 respectively. However, achieving decent yields was a challenge when tris(4-acetamidophenyl)boroxine was used and despite additional catalyst loading, a yield of only 28% of the desired

oxidative Heck product was obtained in the enantioselective reaction even though the yield was very good when the racemic protocol was employed (Entry 7).

Tris(naphthyl)boroxines gave mixed results depending on whether the 1- or 2-substituted analogues were used (Entries 4 and 5). Pleasingly, tris(2-naphthyl)boroxine was well tolerated and yielded 92% of the desired product **201dm** and a decent enantiomeric ratio (Entry 5, 74:26 er). Following on from this result it was thought that perhaps using more sterically hindered tris(1-naphthyl)boroxine may induce higher enantioselectivity. However, neither racemic nor enantioenriched products could be isolated pure and chiral HPLC analysis of the impure products also indicated a very low enantioselectivity of 54:46 er.

Additionally during the course of this work the racemic reaction conditions were applied to substrate **183d** with phenyl boronic acid pinacol ester (Table 42) to investigate the effect on yield. The reaction proceeded in good yield (78%) with only a slight decrease in yield compared to when the boroxine was used (Table 42, Entry 1, 84% cf. Entry 2, 78%). This result proved to be useful during later work on the synthesis of preussidone (section 4.5).



Entry	Arylboron species	Yield (%)[b]
1[c]	Phenyl boroxine	84
2	Phenyl boronic acid pinacol ester	78

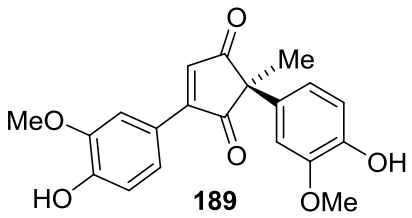
Ligand, solvent and catalyst premixed for 1 h at rt. [a]Equiv. of single aryl group. [b]Isolated yields. [c]Table 41, Entry 6.

Table 42: Comparison between boronic acids and boronic acid pinacol esters

Despite those boroxines which gave poorer yields and enantioselectivity in the boroxine screen (Table 41), results are very promising and demonstrate that a successful enantioselective oxidative Heck reaction has been developed with excellent yields and enantioselectivity for a range of substrates and boroxines. This work certainly indicates potential for further investigation in this area.

4.5 Synthesis of preussidone

Following on from the successful development of the enantioselective oxidative Heck reaction between substituted cyclopentenediones and boroxines as detailed above, our attention turned to examining whether our methodology could be applied to the synthesis of the metabolite preussidone (Figure 10).[13]

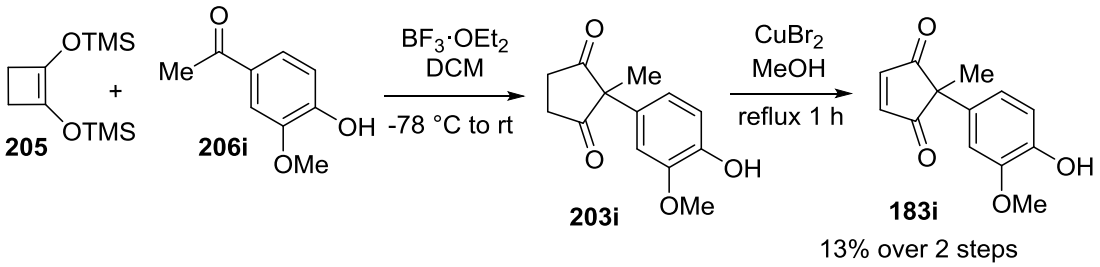


189

Figure 10: (*R*)-Preussidone

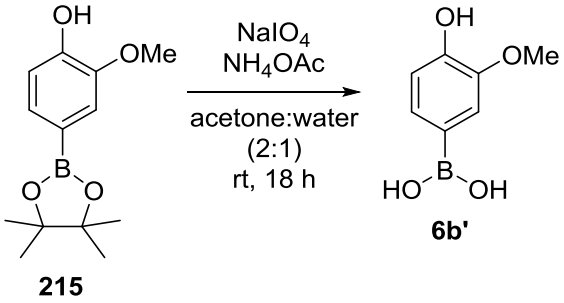
This natural product has been isolated from the fungus *Preussia typharum* and the absolute stereochemistry (*R*) determined by vibrational and electronic circular dichroism.[13] One of the aims of the project was to synthesise preussidone which not only would demonstrate potential application of our methodology, but by comparing the specific rotation of our product and the known literature value, the absolute stereochemistry of our enantioenriched oxidative Heck products could be assigned by analogy.

Firstly, synthesis of the substituted cyclopentenedione substrate **183i** was carried out (Scheme 110). Employing the same methodology used for the synthesis of many of the other substrates used in this project, the appropriate acetophenone **206i** and 1,2-bis((trimethylsilyl)oxy)cyclobut-1-ene **205** were reacted in the presence of Lewis acid $BF_3 \cdot OEt_2$ to synthesise the substrate precursor **203i**. Conversion to **203i** was quite low, most probably due to the unprotected phenol moiety coordinating to $BF_3 \cdot OEt_2$. Nevertheless, we surmised that it was still preferable to having two additional protection and deprotection steps in the synthesis. Due to coelution of the acetophenone starting material **206i** with **203i** on purification by column chromatography, the crude mixture was used for the following oxidation step to synthesise the substrate **183i**.



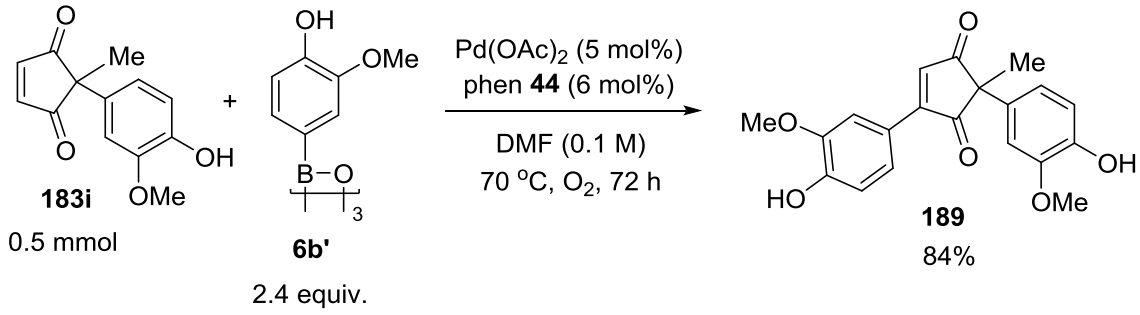
Scheme 110: Synthesis of substrate **183i** for the synthesis of preussidone

Next, our attention turned to synthesising the appropriate boronic acid. Using the commercially available pinacol ester 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **215**, a known literature method for converting a similar boronic ester to the corresponding boronic acid was applied and the boronic acid **6b'** was synthesised (Scheme 111).[37] Purification was a challenge and even following column chromatography and recrystallisation, the boronic acid was not 100% pure. However, it was deemed of sufficient purity to use in the oxidative Heck reaction.



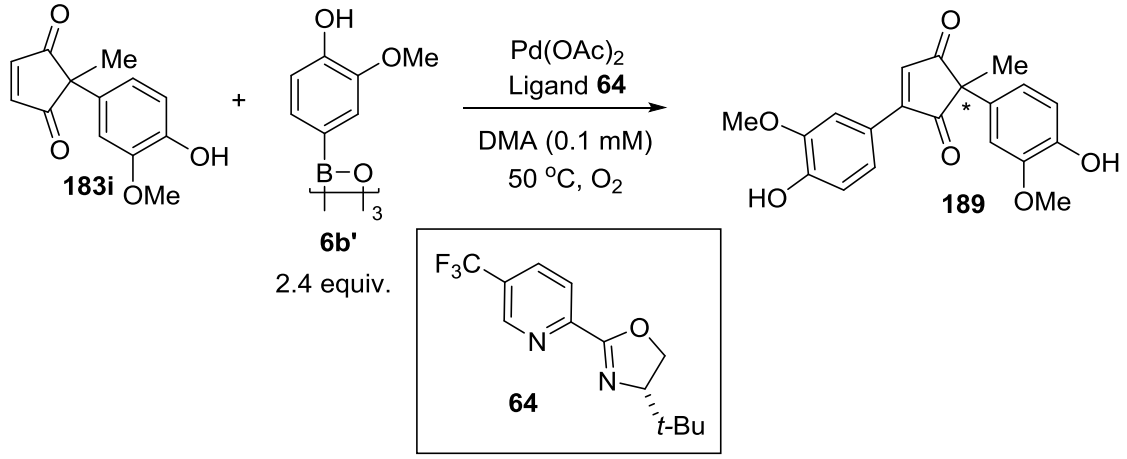
Scheme 111: Synthesis of 4-hydroxy-3-methoxy phenyl boronic acid

Having synthesised the boronic acid **6b'** and substrate **183i**, racemic and enantioselective oxidative Heck reactions were carried out using our previously optimised reaction conditions (Scheme 112).



Scheme 112: Synthesis of preussidone using racemic reaction conditions

Pleasingly, a good isolated yield of 84% was obtained for the racemic reaction to form preussidone **189**. Our attention then turned to carrying out the reaction enantioselectively. Given that in the enantioselective oxidative Heck reactions described previously, the substituted PyOx ligand (*S*)-4-(*tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** has often performed better than the unsubstituted ligand, this was chosen for initial reactions (Table 43).



Entry	$Pd(OAc)_2$	Ligand	Temp.	Time	Yield (%)[a] and er
1	10 mol%	11 mol%	50 °C	94 h	21% 80:20
2	3 portions: 10 + 5 + 5 mol% added at 0, 24, 48 h	3 portions: 11 + 6 + 6 mol% added at 0, 24, 48 h	50 °C	120 h	36% ND
3	3 × 10 mol% added at 0, 30, 54 h	3 × 11 mol% added at 0, 30, 54 h	70 °C	120 h	34% ND
4	4 × 5 mol% added at 0, 7, 22, 31 h	4 × 6 mol% added at 0, 7, 22, 31 h	50 °C	72 h	<58% ND

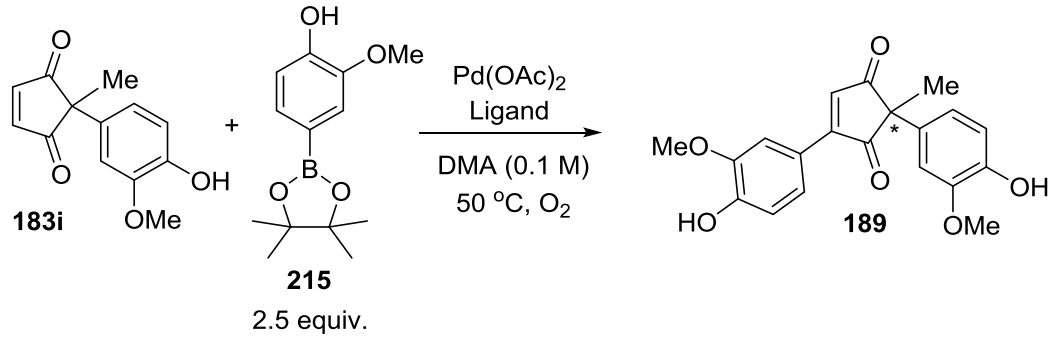
Ligand, solvent and catalyst premixed for 1 h at rt. [a]Isolated yields.

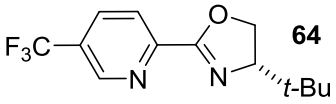
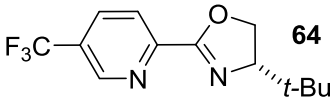
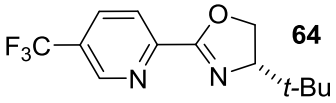
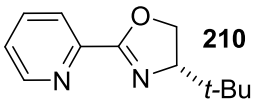
Table 43: Synthesis of preussidone with tris(4-hydroxy-3-methoxyphenyl)boroxine

Using the previously optimised enantioselective reaction conditions (Table 39) regrettably gave poor yield of the desired product **189** (21%) albeit the enantioselectivity was moderately good (80:20 er). In an attempt to increase yield, the catalyst loading was increased to 10 + 5 + 5 mol% added over a period of two days, and

the reaction left for a further three days to maximise conversion. This unfortunately did not increase yield considerably (36%, Entry 2) and therefore the enantiomeric ratio was not obtained. Next, an increase in catalyst and ligand loading to 3 × 10 mol% and 3 × 11 mol% respectively in addition to an increase in the reaction temperature to 70 °C was tried in an attempt to boost yield. Surprisingly, a slight decrease in yield was observed (34%, Entry 3). Given that neither a higher catalyst loading nor an increase in temperature seemed to increase yield, the original optimised reaction temperature of 50 °C was used for the next reaction, coupled with 4 × 5 mol% catalyst and 4 × 6 mol% ligand added over a period of 2 days, and the reaction mixture then left for a further 24 hours (Entry 4). Although the isolated product was not particularly pure, the yield was significantly higher than previous reactions.

Given that the enantioselective synthesis of preussidone had up to this point been hampered by poor yields, we decided that it would be worth including the pinacol ester as a coupling partner in our studies. Although pinacol esters are known to be less reactive than their boronic acid counterparts, and yields using pinacol esters in this work were lower than when the corresponding boronic acid was used (Table 42, Entry 2), using commercially available reagents in our synthesis rather than synthesising the boronic acid would certainly be more advantageous. Results using the pinacol ester as the boron coupling partner are shown in Table 44.



Entry	$Pd(OAc)_2$	Ligand	Time	Yield[a] and er
1	4 × 5 mol% added at 0, 7, 22, 31 h	 **64** 4 × 6 mol% added at 0, 7, 22, 31 h	72 h	69% 84:16
2	10 mol%	 **64** 11 mol%	94 h	<44% ND
3	3 × 5 mol% added at 0, 24 and 48 h	 **64** 3 × 6 mol% added at 0, 24 and 48 h	70 h	79% 85:15
4	3 × 5 mol% added at 0, 24 and 48 h	 **210** 3 × 6 mol% added at 0, 24 and 48 h	70 h	70% 84:16

Ligand, solvent and catalyst premixed for 1 h at rt. [a]Isolated yields.

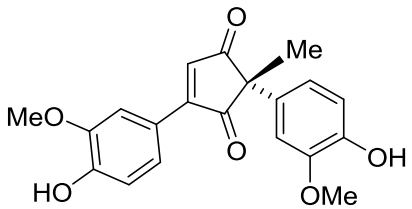
Table 44: Synthesis of Preussidone using pinacol ester 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

Firstly, the reaction conditions which had given the highest yield when the boronic acid was used (<58%, Table 43, Entry 4) were applied to the oxidative Heck reaction using the pinacol ester (Table 44, Entry 1). Surprisingly, given the reduced reactivity of pinacol esters, the yield improved considerably to 69% and a good enantiomeric ratio was obtained also (84:16). This improved yield may possibly be due to difficulties experienced in purification of the boronic acid and simply using a boron coupling partner of higher purity had a positive effect on overall conversion.

In order to attempt to improve the yield further, a number of other reaction conditions were investigated including the optimised enantioselective oxidative Heck conditions (10 mol% catalyst and 11 mol% ligand, Entry 2). The yield unfortunately reduced considerably indicating that portionwise addition of catalyst and ligand was more suited to this reaction. Therefore, we also investigated reducing the catalyst loading to 3 × 5 mol% catalyst and 3 × 6 mol% ligand over 3 days and used both the substituted and unsubstituted PyOx ligands (**64** and **210**, Entries 3 and 4 respectively) to compare to one another and examine the effect on enantioselectivity and yield. Although no considerable improvement was observed to the enantiomeric ratio in either reaction, pleasingly the yield improved and a good yield of 79% was obtained with the substituted PyOx ligand **64** and an enantiomeric ratio of 85:15 (Entry 3).

Preussidone - determining the absolute stereochemistry

As previously mentioned, the absolute stereochemistry of preussidone was determined as (*R*) by vibrational and electronic circular dichroism.[13] Therefore by comparison of the $[\alpha]_D$ value quoted in the literature and that of our synthesised product, by analogy, this would allow the absolute stereochemistry of the products synthesised by the enantioselective oxidative Heck protocol to be assigned. Given that the specific rotation of preussidone is negative and comparing this to the positive value obtained for the specific rotation of preussidone formed synthetically by our methodology, this indicates that the absolute stereochemistry of product **189** is (*S*) (Figure 10). Thereby by analogy we can assume that the enantioenriched products synthesised over the course of this project are also of (*S*) configuration.

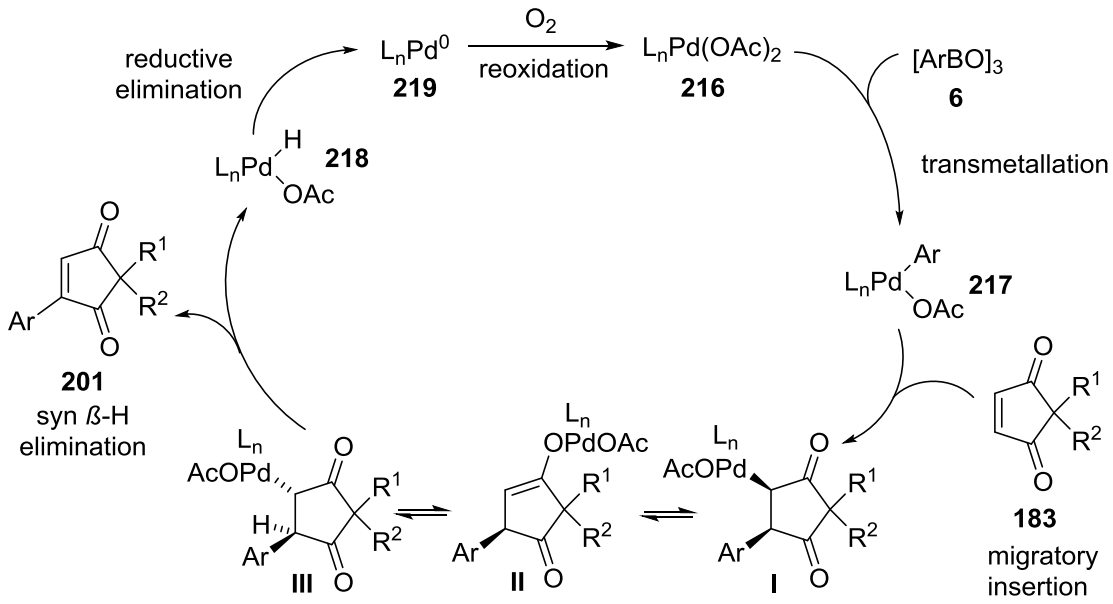


189
(+)-Preussidone
85:15 er

Figure 10: (*S*)-Preussidone

4.6 Reaction mechanism and inducing enantioselectivity

The mechanism for both the racemic and enantioselective reactions is likely to follow a classical oxidative Heck mechanism (Scheme 113).



Scheme 113: Oxidative Heck reaction mechanism

The mechanism commences with transmetallation of the aryl boroxine onto the palladium species **216**. This step is followed by migratory insertion of the substrate onto **217** to form **I**. Epimerisation of this intermediate then occurs, most likely *via* the enolate **II**, to form **III**. This epimerisation allows syn *β*-hydride elimination to occur to form the product **201**. The catalyst is then regenerated *via* reductive elimination of AcOH from **218**, followed by oxidation of **219** to regenerate Pd(II).

In order to rationalise the stereochemistry of the products of the enantioselective oxidative Heck mechanism, current literature can provide valuable insight into the factors affecting selectivity. Stoltz and co-workers have carried out extensive mechanistic studies into palladium-catalysed enantioselective conjugate addition of aryl boronic acids to *β*-substituted cyclic enones, specifically using chiral pyridinooxazoline (PyOx) ligands.[30] Despite the obvious mechanistic differences with our oxidative Heck work, the rationale explaining the stereoselectivity observed (induced during the migratory insertion step) can also be applied to our studies.

The migratory insertion step of the oxidative Heck mechanism also determines the stereoselectivity of the product. Possible transition states for this step need to be

examined in order to provide a justification for the stereochemistry observed (Figure 11). The transition states are four-membered of square planar geometry incorporating the chiral ligand, aryl group from the boronic acid and the alkene substrate.

The transition states are determined by two factors: whether the aryl group of the boronic acid transmetallates *trans* or *cis* to the chiral oxazoline component of the ligand, and the orientation of the substrate on commencing the migratory insertion step.

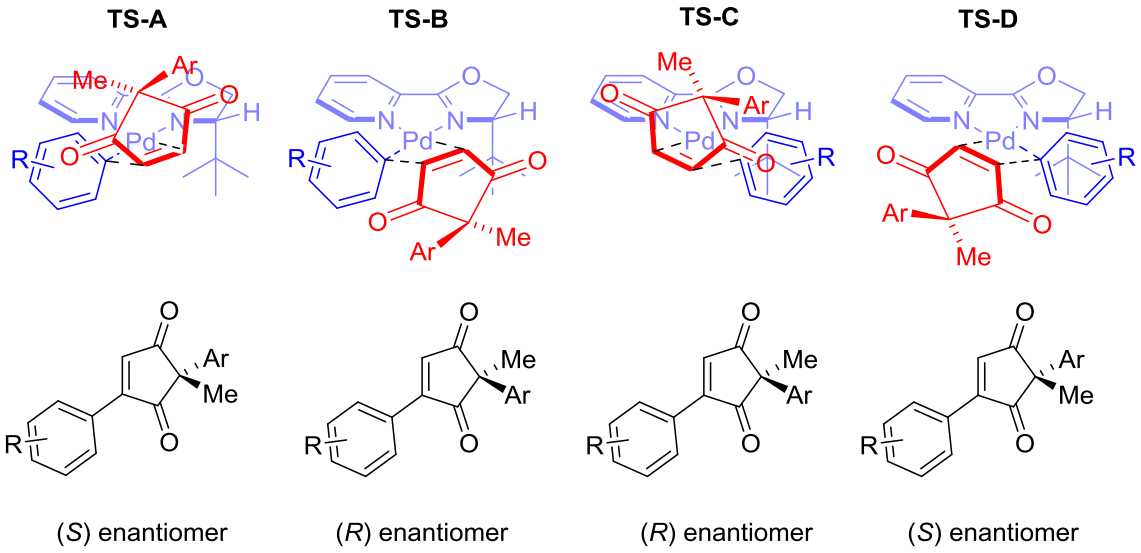


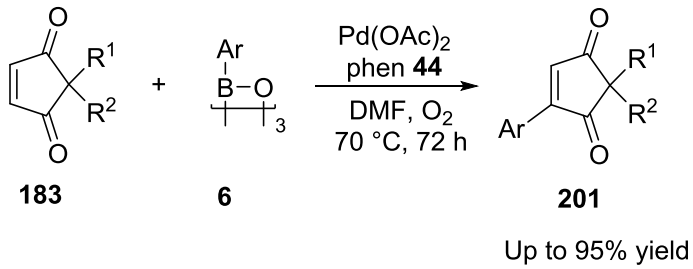
Figure 11: Possible transition states for the migratory insertion step

In addition to the four transition states shown above, a further four are theoretically possible with the alkene approaching the palladium complex facing the opposite way to that indicated resulting in the aryl substituent of the substrate being on the same side as the palladium complex. This would inevitably lead to further steric repulsions and would therefore likely be less favourable than the alkene orientations illustrated in Figure 11.

Of the four transitions states shown, two (**TS-A** and **TS-D**) lead to (*S*) geometry which is observed from our experimental work. Considering steric repulsions between the various components of the transition state, namely the *tert*-butyl group on the oxazoline ring, aryl group from the boronic acid and the substituents on the substrate, it would appear that the configuration of **TS-A** leads to the least steric repulsion of the four possibilities and thus is most likely to be lowest in energy and the transition state through which the mechanism occurs. Further computational studies would obviously be necessary to confirm this hypothesis.

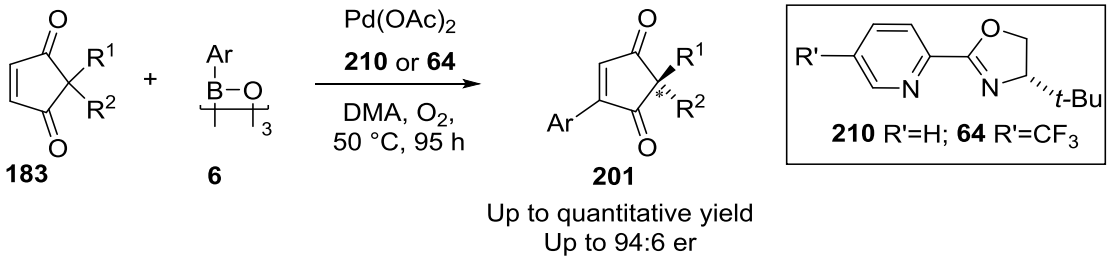
4.7 Conclusions

We have successfully demonstrated that an oxidative Heck reaction can be performed on challenging cyclopentenedione substrates **183** with aryl boronic acids **6** in good yields. A range of substrates and boronic acid coupling partners bearing a wide variety of functional groups are tolerated (Scheme 114).



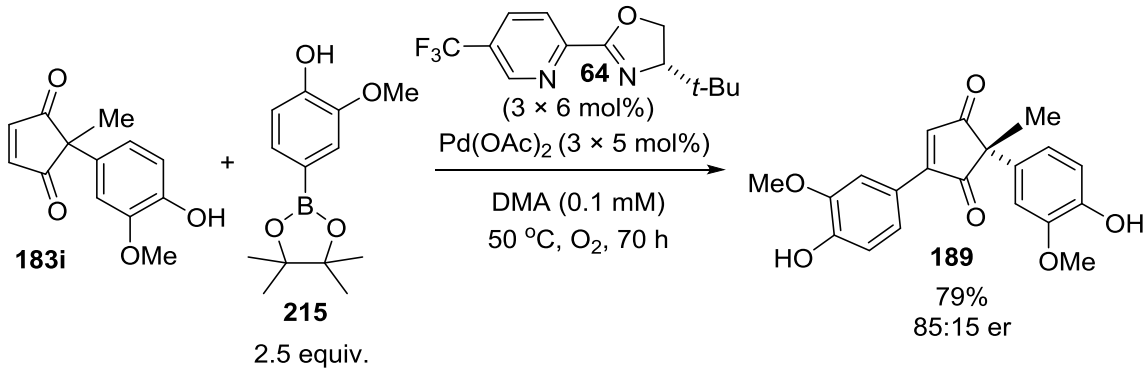
Scheme 114: Enantioselective oxidative Heck reaction on substituted cyclopentenedione substrates with aryl boroxines

Additionally, we have also developed an enantioselective oxidative Heck protocol which we have applied to various substrate and boronic acid combinations to obtain up to quantitative yield and 94:6 enantiomeric ratio (Scheme 115).



Scheme 115: Enantioselective oxidative Heck reaction on substituted cyclopentenedione substrates with aryl boroxines

We have also achieved the third aim of the project by applying our methodology to the synthesis of the (+)-preussidone **189**[13] and by comparison with literature data, we have assigned absolute stereochemistry to our enantioenriched oxidative Heck products (Scheme 116).



Scheme 116: Enantioselective oxidative Heck reaction to synthesise preussidone **189**

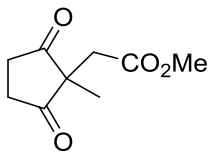
Further work in this area could focus on the enantioselective oxidative Heck reaction in order to increase enantioselectivity given the very promising results we have obtained in our studies so far. Expanding the library of possible substrates to cyclopentenediones bearing two alkyl groups at the 2 position could also be examined in future studies. Additionally, mechanistic studies would also be helpful in order to examine more closely the factors affecting the stereoselectivity in the enantioselective oxidative Heck reaction.

4.8 Experimental Section
General Experimental Section

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26 ppm, δ_C at 77.00 ppm, $(CD_3)_2CO$ at δ_H 2.05 ppm, δ_C at 29.84 ppm or C_6D_6 at δ_H 7.16 ppm, δ_C at 128.06 ppm). *J* values are given in Hz and s, d, dd, t, q, qn and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Enantiomer separation was achieved by chiral stationary phase HPLC with an Agilent Technologies 1120 Compact LC with either CHIRALPAK IA or IB column as appropriate. Alternatively, where specified, enantiomeric ratios were calculated using chiral shift reagent (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol, purchased from Sigma-Aldrich. Optical rotation was measured on a Bellingham and Stanley ADP410 polarimeter. Petrol ether refers to petroleum ether (40–60 ^{o}C). Anhydrous DMF and DMA were purchased from Sigma-Aldrich and Fluorochem respectively and used without further purification. All arylboronic acids were purchased from Sigma-Aldrich, Fluorochem or Acros, and better results are achieved if they are heated under vacuum with a heat gun prior to the oxidative Heck reaction. The oxidative Heck reactions were carried out in dried glassware, using anhydrous DMF and $Pd(OAc)_2$ from Johnson Matthey.

Synthesis of 2,2-Disubstituted Cyclopentene-1,3-dione Starting Materials:

Methyl 2-(1-methyl-2,5-dioxocyclopentyl)acetate[38] (203c)

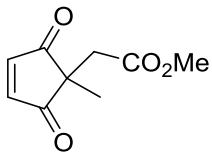


203c

To a suspension of 2-methylcyclopentane-1,3-dione **202** (5.00 g, 44.6 mmol, 1 equiv.) and TBAI (8.20 g, 43.4 mmol, 0.1 equiv.) in anhydrous CH_3CN (233 mL), DBU (7.7 mL, 51.6 mmol, 1.2 equiv.) was added dropwise at 0 °C. After the solution was warmed to room temperature, methylbromoacetate **204** (6.8 mL, 71.4 mmol, 1.6 equiv.) was added and the reaction was refluxed for 40 h. The reaction was quenched with H_2O. The aqueous layer was washed with EtOAc until the organic layer was colourless. The combined organic layers were dried over $MgSO_4$ before the solvent was removed with reduced pressure. The resulting residue was purified by silica gel column chromatography (petrol ether/EtOAc, 10:1→1.5:1) to obtain methyl 2-(1-methyl-2,5-dioxocyclopentyl)acetate **203c** (1.82 g, 9.88 mmol, 22%) as a yellow crystalline solid.

Data provided by C. Lamb: M.p. 94 – 96 °C; R_f = 0.2 (3:1 petrol ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.55 (s, 3H, OCH_3), 2.89 (s, 2H, CH_2), 2.83 (s, 4H, CH_2CH_2), 1.04 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.9 (C), 171.9 (C), 52.7 (C), 52.2 (CH_3), 39.8 (CH_2), 34.6 (CH_2), 19.8 (CH_3); ν_{max}/cm^{-1} 2958, 1762, 1712, 1408, 1398, 1213, 1153, 1075, 997, 799.

Methyl 2-(1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate[16] (183c)



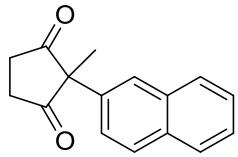
183c

To a flask containing $CuBr_2$ (3.19 g, 14.3 mmol, 2.2 equiv.), methyl 2-(1-methyl-2,5-dioxocyclopentyl)acetate **203c** (1.20 g, 6.52 mmol, 1 equiv.) dissolved in anhydrous MeOH (46 mL) was added. The reaction was left to reflux for 18 h. The reaction was quenched with H_2O and acidified with HCl (2 mL, 1M). The aqueous layer was extracted with Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (petrol ether/EtOAc, 15:1→5:1) to obtain methyl 2-(1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate **183c** (0.980 g, 5.83 mmol, 83%) as a yellow crystalline solid.

Data provided by C. Lamb: M.p. 73-74 °C; R_f = 0.5 (3:1 petrol ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (s, 2H, HC=CH), 3.55 (s, 3H, CH_3), 2.86 (s, 2H, CH_2),

1.14 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.7 (C), 170.8 (C), 147.5 (CH), 52.0 (CH_3), 47.7 (C), 37.4 (CH_2), 20.5 (CH_3); ν_{max}/ cm^{-1} 3070 w, 2955 w, 1729 str, 1698 v str, 1442 m, 1403 w, 1355 str, 1207 v str, 1187 v str, 1006 m, 862 m, 701m.

2-Methyl-2-(naphthalen-2-yl)cyclopentane-1,3-dione (203d)[16]

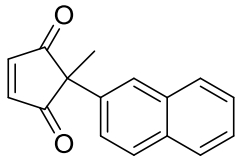


203d

2'-Acetonaphthone (2.46 g, 0.0145 mol, 1 equiv.) and 1,2-bis(trimethylsiloxy)cyclobutene **205** (5.6 mL, 0.0218 mol, 1.5 equiv.) were added to dichloromethane (37 mL), followed by $BF_3{\cdot}OEt_2$ (2.7 mL, 0.0219 mol, 1.5 equiv.) at 0 °C. The solution was warmed to room temperature and stirred for 20 h under an inert atmosphere. Water (10 mL) was added and the reaction left to stir for 50 min. The organic layer was separated and the aqueous layer was washed with dichloromethane (3 × 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography (10:1 hexane:EtOAc) to yield 2-methyl-2-(naphthalen-2-yl)cyclopentane-1,3-dione[16] **203d** as a yellow oil (1.98 g, 0.00830 mol, 57%).

R_f = 0.27 (2:1 hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 – 7.73 (m, 3H, Ar-H), 7.63 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.51 – 7.43 (m, 2H, Ar-H), 7.38 (dd, *J* = 8.7, 2.0 Hz, 1H, Ar-H), 3.03 – 2.61 (m, 4H, CH_2), 1.52 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.9 (C), 134.2 (C), 133.2 (C), 132.5 (C), 129.2 (CH), 127.9 (CH), 127.4 (CH), 126.53 (CH), 126.47 (CH), 125.5 (CH), 123.6 (CH), 62.0 (C), 35.2 (CH_2), 19.7 (CH_3); HRMS (APCI) *m/z calc*. for $C_{16}H_{15}O_2$: 239.1067 $[M+H]^+$; found: 239.1064.

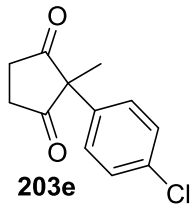
2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione (183d)[16]


183d

2-Methyl-2-(naphthalen-2-yl)cyclopentane-1,3-dione **203d** (1.04 g, 4.37 mmol, 1 equiv.) was added to anhydrous MeOH (34 mL) followed by $CuBr_2$ (2.17 g, 9.71 mmol, 2.2 equiv.). The resulting reaction mixture was refluxed for 2 h before being quenched with cold H_2O and 1 M HCl. Et_2O was added to the solution and the layers separated. The aqueous layer was washed with Et_2O (4 × 30 mL) and the combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting residue was purified by silica gel column chromatography (10:1 → 5:1 hexane:EtOAc) to give 2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** as a yellow solid (791.5 mg, 3.35 mmol, 77%).

M. p. 97-98 °C; R_f = 0.27 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 – 7.77 (3 H, m, Ar-H), 7.73 (1 H, d, *J* = 1.8 Hz, Ar-H), 7.53 – 7.41 (3 H, m, Ar-H), 7.39 (2 H, s, =CH), 1.68 (3 H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.8 (C), 148.3 (CH), 134.1 (C), 133.2 (C), 132.5 (C), 128.7 (CH), 128.1 (CH), 127.5 (CH), 126.4 (2 × CH), 125.7 (CH), 124.0 (CH), 54.7 (C), 19.8 (CH_3); HRMS (APCI) *m/z calc*. for $C_{16}H_{13}O_2$: 237.0910 $[M+H]^+$; found: 237.0909.

2-(4-Chlorophenyl)-2-methylcyclopentane-1,3-dione (203e)

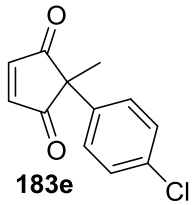

203e

4'-Chloroacetophenone (0.310 g, 2.00 mmol, 1 equiv.) and 1,2-bis(trimethylsiloxy)cyclobutene **205** (0.77 mL, 3.00 mmol, 1.5 equiv.) were added to dichloromethane (5.1 mL), followed by $BF_3{\cdot}OEt_2$ (0.37 mL, 3.00 mmol, 1.5 equiv.) at 0 °C. The solution was warmed to room temperature and stirred for 16 h under an inert atmosphere. Water (10 mL) was added and the reaction left to stir for 30 min. The organic layer was separated and the aqueous layer was washed with dichloromethane (3 × 15 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography (10:1 hexane:EtOAc) to yield 2-(4-chlorophenyl)-2-methylcyclopentane-1,3-dione **203e** as a colourless oil, (0.1994 g, 0.90 mmol, 45%).

R_f = 0.48 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.11 – 2.58 (m, 4H, H_2C-CH_2), 1.42 (s, 3H,

CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.7 (C), 135.3 (C), 134.2 (C), 129.4 (CH), 127.8 (CH), 61.0 (C), 35.2 (CH_2), 20.1 (CH_3); ν_{max}/cm^{-1} 2976 w, 2930 w, 1765 w, 1721 v str, 1491 str, 1260 m, 1095 str, 1013 str, 990 m, 828 str; HRMS (APCI) *m/z calc*. For $C_{12}H_{12}O_2Cl$: 223.0520 $[M+H]^+$; found: 223.0520.

2-(4-Chlorophenyl)-2-methylcyclopent-4-ene-1,3-dione (183e)

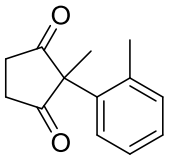


183e

2-(4-Chlorophenyl)-2-methylcyclopentane-1,3-dione (**203e**) (188.5 mg, 0.846 mmol, 1 equiv.) was added to a solution of $CuBr_2$ (420.8 mg, 1.88 mmol, 2.2 equiv.) in anhydrous MeOH (7 mL). The resulting reaction mixture was refluxed for 3 h before being quenched with cold H_2O and 1 M HCl. Et_2O was added to the solution. The aqueous layer was washed with Et_2O until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4 before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 7:1→5:1) to yield 2-(4-chlorophenyl)-2-methylcyclopent-4-ene-1,3-dione **183e** (107.4 mg, 0.487 mmol, 58%) as a yellow oil.

R_f = 0.13 (2:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 2H, alkene-H), 7.31 – 7.27 (m, 2H, Ar-H), 7.25 – 7.21 (m, 2H, Ar-H), 1.54 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.5 (C), 148.3 (CH), 135.2 (C), 133.9 (C), 129.0 (CH), 127.9 (CH), 53.8 (C), 20.1 (CH_3); ν_{max}/cm^{-1} 3072 w, 2973 w, 1699 v str, 1492 str, 1095 m, 1012 str, 833 m, 805 m, 728 m; HRMS (APCI) *m/z calc*. For $C_{12}H_{10}O_2Cl$: 221.0364 $[M+H]^+$; found: 221.0365.

2-Methyl-2-(*o*-tolyl)cyclopentane-1,3-dione (203f)



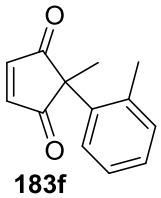
203f

2'-Methylacetophenone (267 mg, 1.99 mmol, 1 equiv.) and $BF_3{\cdot}OEt_2$ (0.51 mL, 4.13 mmol, 2.0 equiv.) were added to dichloromethane (20 mL) at –78 °C and the solution stirred for 30 min. 1,2-Bis(trimethylsiloxy)cyclobutene **205** (0.91 mL, 3.54 mmol, 1.8 equiv.) was added and the solution was warmed to room temperature and stirred for 18 h under an inert atmosphere. Additional portions of 1,2-bis(trimethylsiloxy)cyclobutene **205** (0.51 mL, 1.99 mmol, 1.0 equiv.) and $BF_3{\cdot}OEt_2$ (0.26 mL, 2.11 mmol, 1.1 equiv.) were

added at –78 °C and the solution allowed to warm to room temperature and stirred for a further 4 h. Water (10 mL) and $BF_3{\cdot}OEt_2$ (0.5 mL) were added. Followed by Na_2CO_3 (10 mL) and $CHCl_3$ (10 mL). The organic layers were separated and the aqueous layer was washed with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography (10:1→2:1 hexane:EtOAc) to yield 2-methyl-2-(*o*-tolyl)cyclopentane-1,3-dione **203f** as a colourless amorphous solid (144.6 mg, 0.715 mmol, 36%).

White solid; Decomposes at 136 °C; R_f = 0.14 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.30 (m, 1H, Ar-H), 7.29 – 7.21 (m, 2H, Ar-H), 7.19 – 7.14 (m, 1H, Ar-H), 3.23 – 2.87 (m, 4H, H_2C-CH_2), 1.95 (s, 3H, CH_3), 1.62 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 213.9 (C), 135.6 (C), 135.1 (C), 131.3 (CH), 128.3 (CH), 128.2 (CH), 126.4 (CH), 62.8 (C), 34.9 (CH_2), 21.6 (CH_3), 20.3 (CH_3); ν_{max}/ cm^{-1} 3024 w, 2926 w, 1715 v str, 1464 m, 1413 w, 1271 w, 1162 w, 1062 m, 1039 m, 999 w, 744 v str, 717 m; HRMS (NSI) *m/z calc*. For $C_{13}H_{18}O_2N$: 220.1332 $[M+NH_4]^+$; found: 220.1333.

2-Methyl-2-(*o*-tolyl)cyclopent-4-ene-1,3-dione (183f)



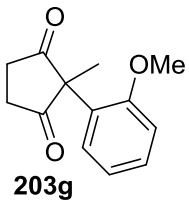
183f

2-Methyl-2-(*o*-tolyl)cyclopentane-1,3-dione **203f** (144.6 mg, 0.715 mmol, 1 equiv.) was added to a solution of $CuBr_2$ (355.5 mg, 1.592 mmol, 2.2 equiv.) in anhydrous MeOH (8 mL). The resulting reaction mixture was refluxed for 1 h before being quenched with cold H_2O and 1 M HCl. Et_2O was added to the solution. The aqueous layer was washed with Et_2O until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$ before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to yield 2-methyl-2-(*o*-tolyl)cyclopent-4-ene-1,3-dione **183f** (112.4 mg, 0.5614 mmol, 79%) as a yellow oil.

Yellow crystalline solid; M pt. 71-73 °C; R_f = 0.65 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 7.7, 1.6 Hz, 1H, Ar-H), 7.31 (s, 2H, alkene-H), 7.30 – 7.19 (m, 2H, Ar-H), 7.11 – 7.06 (m, 1H, Ar-H), 2.01 (s, 3H, CH_3), 1.67 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.2 (C), 146.3 (CH), 135.9 (C), 134.1 (C), 131.5

(CH), 128.9 (CH), 128.3 (CH), 126.5 (CH), 56.3 (C), 22.0 (CH_3), 21.7 (CH_3); ν_{max}/ cm^{-1} 3082 w, 2969 w, 1698 v str, 1457 m, 1316 w, 1267 m, 1182 m, 1035 m, 850 str, 772 m, 760 v str; HRMS (NSI) *m/z calc*. For $C_{13}H_{16}O_2N$: 218.1176 $[M+NH_4]^+$; found: 218.1177.

2-(2-Methoxyphenyl)-2-methylcyclopentane-1,3-dione (203g)[39]

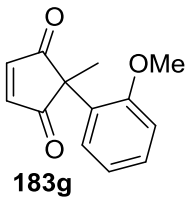


203g

2'-Methoxyacetophenone (310 mg, 2.03 mmol, 1 equiv.) and $BF_3{\cdot}OEt_2$ (0.51 mL, 4.13 mmol, 2.0 equiv.) were added to dichloromethane (20 mL) at –78 °C and the solution stirred for 30 min. 1,2-Bis(trimethylsiloxy)cyclobutene **205** (0.91 mL, 3.54 mmol, 1.8 equiv.) was added and the solution was warmed to room temperature and stirred for 18 h under an inert atmosphere. Additional portions of 1,2-bis(trimethylsiloxy)cyclobutene **205** (0.51 mL, 1.99 mmol, 1.0 equiv.) and $BF_3{\cdot}OEt_2$ (0.26 mL, 2.11 mmol, 1.1 equiv.) were added at –78 °C and the solution allowed to warm to room temperature and stirred for a further 5 h. Water (10 mL) was added and the reaction left to stir for 1 h. The organic layers were separated and the aqueous layer was washed with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography (10:1→2:1 hexane:EtOAc) to yield 2-(2-methoxyphenyl)-2-methylcyclopentane-1,3-dione **203g** as a colourless amorphous solid (148.5 mg, 0.680 mmol, 34%).

R_f = 0.35 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 7.30 (ddd, *J* = 8.1, 7.6, 1.6 Hz, 1H, Ar-H), 7.04 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 6.81 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar-H), 3.70 (s, 3H, OCH_3), 3.04 – 2.84 (m, 4H, H_2C-CH_2), 1.49 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 215.3 (C), 154.6 (C), 129.3 (CH), 128.1 (CH), 127.8 (C), 121.5 (CH), 110.7 (CH), 57.8 (C), 55.2 (CH_3), 35.0 (CH_2), 17.7 (CH_3); ν_{max}/cm^{-1} 2941 w, 1714 v str, 1490 str, 1459 str, 1259 v str, 1243 v str, 1188 m, 1021, str, 761 v str; HRMS (APCI) *m/z calc*. For $C_{13}H_{15}O_3$: 219.1016 $[M+H]^+$; found: 219.1017.

2-(2-Methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione (183g)

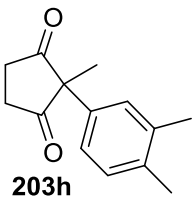


183g

2-(2-Methoxyphenyl)-2-methylcyclopentane-1,3-dione (**203g**) (143.0 mg, 0.655 mmol, 1 equiv.) was added to a solution of $CuBr_2$ (324.8 mg, 1.454 mmol, 2.2 equiv.) in anhydrous MeOH (7 mL). The resulting reaction mixture was refluxed for 16 h before being quenched with cold H_2O and 1 M HCl. Et_2O was added to the solution. The aqueous layer was washed with Et_2O until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4 before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 7:1→5:1) to yield 2-(2-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **183g** (112.7 mg, 0.5212 mmol, 80%) as a yellow solid.

M.p. 105-107 °C; R_f = 0.25 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 7.29 (ddd, *J* = 8.2, 7.6, 1.6 Hz, 1H, Ar-H), 7.20 (s, 2H, alkene-H), 7.03 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-H), 6.76 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 3.58 (s, 3H, OCH_3), 1.55 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.7 (C), 156.0 (C), 145.0 (CH), 129.5 (CH), 129.1 (CH), 125.4 (C), 121.4 (CH), 110.7 (CH), 55.0 (CH_3), 53.3 (C), 18.9 (CH_3); ν_{max}/cm^{-1} 2972 w, 1697 v str, 1493 m, 1457 m, 1264 m, 1245 m, 1036 str, 1017 m, 845 m, 746 v str; HRMS (NSI) *m/z calc*. For $C_{13}H_{13}O_3$: 217.0859 $[M+H]^+$; found: 217.0862.

2-(3,4-Dimethylphenyl)-2-methylcyclopentane-1,3-dione (203h)



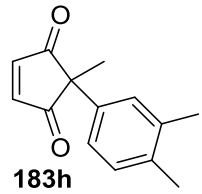
203h

3',4'-Dimethylacetophenone (1.00 g, 6.75 mmol, 1 equiv.) was added to dichloromethane (70 mL) at –78 °C followed by $BF_3{\cdot}OEt_2$ (1.66 mL, 13.46 mmol, 2.0 equiv.) and the solution stirred for 30 min. 1,2-Bis(trimethylsiloxy)cyclobutene **205** (3.12 mL, 12.15 mmol, 1.8 equiv.) was then added, the solution was warmed to room temperature and stirred for 18 h under an inert atmosphere. $BF_3{\cdot}OEt_2$ (2 mL) was added followed by Na_2CO_3 (20 mL), water (20 mL) and chloroform (20 mL). The organic layer was separated and the aqueous layer was washed with chloroform (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography (10:1 hexane:EtOAc) to yield

2-(3,4-dimethylphenyl)-2-methylcyclopentane-1,3-dione **203h** (982 mg, 4.54 mmol, 67%).

M.p. 70-72 °C; R_f = 0.24 (2:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, J = 7.9 Hz, 1H, Ar-H), 6.97 – 6.87 (m, 2H, Ar-H), 3.03 – 2.58 (m, 4H, H_2C-CH_2), 2.22 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.1 (C), 137.7 (C), 136.6 (C), 134.3 (C), 130.4 (CH), 127.3 (CH), 123.6 (CH), 61.9 (C), 35.2 (CH_2), 19.8 (CH_3), 19.5 (CH_3), 19.2 (CH_3); ν_{max}/cm^{-1} 2977 w, 2931 w, 1759 m, 1716 v str, 1608 w, 1500 m, 1447 m, 1417 w, 1267 m, 1120 m, 1076 str, 1022 str, 991 str, 818 str, 715 m; HRMS (APCI) *m/z calc*. For $C_{14}H_{17}O_2$: 217.1223 $[M+H]^+$; found: 217.1223.

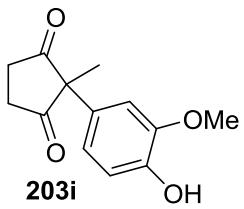
2-(3,4-Dimethylphenyl)-2-methylcyclopent-4-ene-1,3-dione (183h)


183h

2-(3,4-Dimethylphenyl)-2-methylcyclopentane-1,3-dione **203h** (982.2 mg, 4.541 mmol, 1 equiv.) was added to a solution of $CuBr_2$ (2.26 g, 10.12 mmol, 2.2 equiv.) in anhydrous MeOH (51 mL). The resulting reaction mixture was refluxed for 1 h before being quenched with cold H_2O and 1 M HCl. Et_2O was added to the solution. The aqueous layer was washed with Et_2O until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$ before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 10:1) to yield 2-(3,4-dimethylphenyl)-2-methylcyclopent-4-ene-1,3-dione **183h** (728.1 mg, 3.398 mmol, 75%) as a yellow crystalline solid.

M.p. 73-74 °C; R_f = 0.32 (2:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (s, 2H, alkene-H), 7.08 (d, J = 7.7 Hz, 1H, Ar-H), 7.04 – 6.96 (m, 2H, Ar-H), 2.22 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 1.55 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2 (C), 148.3 (CH), 137.1 (C), 136.3 (C), 134.2 (C), 130.0 (CH), 127.5 (CH), 123.7 (CH), 54.3 (C), 19.9 (CH_3), 19.4 (CH_3), 19.3 (CH_3); ν_{max}/cm^{-1} 3058 w, 2973 w, 1740 w, 1697 v str, 1608 w, 1503 w, 1444 w, 1330 w, 1253 m, 1047 m, 874 str, 815 m, 711 w; HRMS (APCI) *m/z calc*. For $C_{14}H_{18}O_2N$: 232.1332 $[M+NH_4]^+$; found: 232.1327.

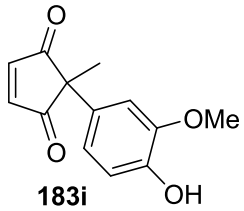
2-(4-Hydroxy-3-methoxyphenyl)-2-methylcyclopentane-1,3-dione (203i)



203i

4'-Hydroxy-3'-methoxyacetophenone (1.0044 g, 6.044 mmol, 1 equiv.), was added to dichloromethane (60 mL) at –78 °C followed by $BF_3{\cdot}OEt_2$ (1.85 mL, 15.00 mmol, 2.5 equiv.) and the solution stirred for 30 min. 1,2-Bis(trimethylsiloxy)cyclobutene **205** (2.79 mL, 10.9 mmol, 1.8 equiv.) was then added, the solution was warmed to room temperature and stirred for 16 h under an inert atmosphere. $BF_3{\cdot}OEt_2$ (1.5 mL) was added followed by Na_2CO_3 (20 mL), water (20 mL) and chloroform (20 mL). The organic layer was separated and the aqueous layer was washed with chloroform (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography (5:1→1:1 hexane:EtOAc). Pure product **203i** could not be purified due to coelution with 4'-hydroxy-3'-methoxyacetophenone. Therefore the mixture was used for the following step to synthesise 2-(4-hydroxy-3-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **183i.**

2-(4-Hydroxy-3-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione (183i)



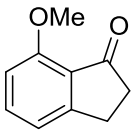
183i

A crude mixture of 2-(4-hydroxy-3-methoxyphenyl)-2-methylcyclopentane-1,3-dione **203i** from the previous step (0.455 g, 1.94 mmol, 1 equiv.) was added to a solution of $CuBr_2$ (0.964 g, 4.32 mmol, 2.2 equiv.) in anhydrous MeOH (22 mL). The resulting reaction mixture was refluxed for 16 h before being quenched with cold H_2O and 1 M HCl. Et_2O was added to the solution. The aqueous layer was washed with Et_2O until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1→3:1) followed by recrystallisation to yield 2-(4-hydroxy-3-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **183i** (98.5 mg, 0.424 mmol, 13% over two steps) as a yellow crystalline solid.

M.p. 131-132 °C; R_f = 0.22 (1:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 2H, alkene-H), 6.87 – 6.81 (m, 2H, Ar-H), 6.74 (dd, J = 8.4, 2.1 Hz, 1H, Ar-H), 5.57 (s, 1H, O<u>H</u>), 3.88 (s, 3H, CH_3), 1.54 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ =

205.1 (C), 148.1 (CH), 146.7 (C), 145.3 (C), 128.5 (C), 119.4 (CH), 114.5 (CH), 109.0 (CH), 55.9 (CH_3), 53.9 (C), 20.1 (CH_3); ν_{max}/cm^{-1} 3320 br str, 2941 w, 1693 v str, 1598 w, 1516 v str, 1524 m, 1257 v str, 1240 v str, 1135 str, 1030 v str, 858 m, 836 str, 779 m; HRMS (APCI) *m/z calc*. For $C_{13}H_{13}O_4$: 233.0808 $[M+H]^+$; found: 233.0812.

7-Methoxy-2,3-dihydro-1H-inden-1-one (208)[40]

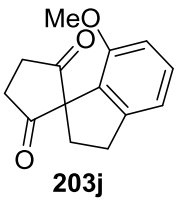


208

7-Hydroxy-1-indanone **207** (0.508 g, 3.41 mmol, 1 equiv.), K_2CO_3 (0.950 g, 6.88 mmol, 2.0 equiv.) and methyl iodide (0.25 mL, 4.0 mmol, 1.2 equiv.) were added to acetone (50 mL) and tetrahydrofuran (30 mL) and refluxed for 20 h. Upon completion, brine (50 mL) and dichloromethane (50 mL) were added and the phases separated. The aqueous phase was washed with dichloromethane (4 × 50 mL) and the organic layers combined, dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo* to yield 7-methoxy-2,3-dihydro-1H-inden-1-one **208** as colourless crystals (0.553 g, 3.41 mmol, 100%).

M.p. 99-100 °C; R_f = 0.36 (1.5:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 8.2, 7.6 Hz, 1H, Ar-H), 7.01 (dd, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 6.78 (dd, *J* = 8.2, 0.8 Hz, 1H, Ar-H), 3.95 (s, 3H, CH_3), 3.15 – 3.01 (m, 2H, CH_2), 2.70 – 2.63 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.7 (C), 158.2 (C), 157.9 (C), 136.3 (CH), 125.2 (C), 118.4 (CH), 108.8 (CH), 55.7 (CH_3), 36.8 (CH_2), 25.5 (CH_2); HRMS (APCI) *m/z calc*. For $C_{10}H_{11}O_2$: 163.0754 $[M+H]^+$; found: 163.0750.

7'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione (203j)



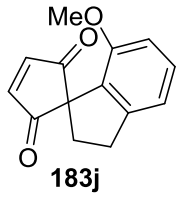
203j

7-Methoxy-2,3-dihydro-1H-inden-1-one **208** (0.481 g, 2.96 mmol, 1 equiv.), was added to dichloromethane (29 mL) at –78 °C followed by $BF_3{\cdot}OEt_2$ (0.75 mL, 6.08 mmol, 2.1 equiv.) and the solution stirred for 45 min. 1,2-Bis(trimethylsiloxy)cyclobutene **205** (1.35 mL, 5.24 mmol, 1.8 equiv.) was then added, the solution was warmed to room temperature and stirred for 18 h under an inert atmosphere. Upon completion, $BF_3{\cdot}OEt_2$ (1 mL) was added followed by Na_2CO_3 (20 mL), water (20 mL) and chloroform (20 mL). The organic layer was separated and the aqueous layer was washed with chloroform (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the

solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography (5:1→1:1 hexane:EtOAc) to yield 7'-methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione **203j** as a white crystalline solid (158.1 mg, 0.688 mmol, 23%).

M.p. 104-105 °C; R_f = 0.57 (1.5:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (dd, *J* = 8.1, 7.6 Hz, 1H, Ar-H), 6.89 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar-H), 6.67 – 6.57 (m, 1H, Ar-H), 3.72 (s, 3H, CH_3), 3.18 (app. t, *J* = 7.4 Hz, 2H, CH_2),* 3.12 – 2.95 (m, 2H, CH_2), 2.91 – 2.74 (m, 2H, CH_2), 2.39 – 2.29 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 215.6 (C), 154.2 (C), 147.7 (C), 130.3 (C), 130.2 (CH), 117.6 (CH), 108.5 (CH), 65.9 (C), 55.3 (CH_3), 36.5 (CH_2), 35.5 (CH_2), 32.5 (CH_2); ν_{max}/cm^{-1} 2938 w, 2839 w, 1715 v str, 1601 w, 1586 m, 1477 m, 1440 w, 1268 str, 1173 m, 1074 str, 777 v str; HRMS (NSI) *m/z calc*. For $C_{14}H_{15}O_3$: 231.1016 $[M+H]^+$; found: 231.1019.

7'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione (183j)[41]



183j

7'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione **203j** (158.1 mg, 0.6879 mmol, 1 equiv.) was added to a solution of $CuBr_2$ (0.342 g, 1.53 mmol, 2.2 equiv.) in anhydrous MeOH (8 mL). The resulting reaction mixture was refluxed for 3 h before being quenched with cold H_2O and 1 M $HCl{\cdot}Et_2O$ was added to the solution. The aqueous layer was washed with Et_2O until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$ before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 5:1→3:1) to yield 7'-methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione **183j** (123.7 mg, 0.5425 mmol, 79%) as a yellow crystalline solid.

M.p. 101-103 °C; R_f = 0.26 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 2H, alkene-H), 7.21 (dd, *J* = 8.2, 7.6 Hz, 1H, Ar-H), 6.90 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar-H), 6.59 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar-H), 3.62 (s, 3H, CH_3), 3.18 (app. t, *J* = 7.5 Hz, 2H, CH_2),* 2.32 (t, *J* = 7.5 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.0 (C), 155.1 (C), 148.3 (C), 147.9 (CH), 130.4 (CH), 127.5 (C), 117.4 (CH), 108.4 (CH), 61.2

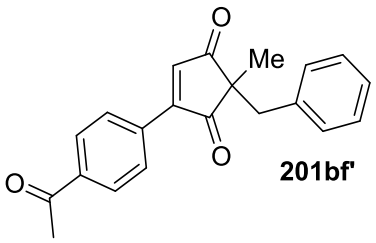
* ^{1}H NMR signal for **203j** and **183j** at 3.18 ppm is an AB spectrum corresponding to diastereotopic CH_2 protons.

(C), 55.2 (CH_3), 34.1 (CH_2), 32.2 (CH_2); HRMS (NSI) *m/z calc*. For $C_{14}H_{13}O_3$: 229.0859 $[M+H]^+$; found: 229.0862.

Oxidative Heck Reactions:

Boronic acid screen

4-(4-Acetylphenyl)-2-benzyl-2-methylcyclopent-4-ene-1,3-dione (201bf')



201bf'

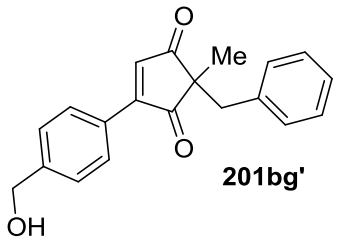
4-Acetylphenyl boronic acid **6f'** (36.3 mg, 0.221 mmol, 2.2 equiv.) was heated (heat gun) under vacuum to convert it to the boroxine before a N_2 environment was introduced. 2-Benzyl-2-methylcyclopent-4-ene-1,3-dione **183b** (19.9 mg, 0.0995 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.3 mg, 5.8 μmol, 0.06 equiv.) were added in order, with a N_2 environment being re-introduced after each addition. Anhydrous DMF (1 mL) was then added before the resulting solution was allowed to stir at 70 °C in an O_2 environment (balloon) for 24 h. The reaction was removed from the heat for further addition of 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.3 mg, 5.8 μmol, 0.06 equiv.) and left to stir at 70 °C under an O_2 atmosphere for a further 17 h. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc, gradient 25:1 to 10:1) to yield **201bf'** (17.3 mg, 53.4 μmol, 54%) as a yellow oil.

R_f = 0.24 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 – 7.92 (m, 2H, Ar-H), 7.78 – 7.69 (m, 2H, Ar-H), 7.16 – 7.04 (m, 4H, Ar-H and =CH), 7.00 – 6.91 (m, 2H, Ar-H), 3.07 (app. s, 2H, CH_2),* 2.61 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9 (C), 205.3 (C), 197.2 (C), 155.9 (C), 142.3 (CH), 138.6 (C),

* ^{1}H NMR signal at 3.07 ppm is an AB spectrum corresponding to diastereotopic CH_2 protons.

135.6 (C), 133.0 (C), 129.6 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 127.1 (CH), 54.0 (C), 41.7 (CH_2), 26.7 (CH_3), 19.3 (CH_3); ν_{max}/cm^{-1} 3084 w, 2921 w, 1737 w, 1689 v str, 1593 w, 1555 w, 1454 w, 1356 w, 1262 str, 1237 m, 1017 w, 958 w, 837 str, 757 m, 701 str; HRMS (NSI) *m/z calc*. for $C_{21}H_{19}O_3$: 319.1329 $[M+H]^+$; found: 319.1333.

2-Benzyl-4-(4-(hydroxymethyl)phenyl)-2-methylcyclopent-4-ene-1,3-dione (201bg')



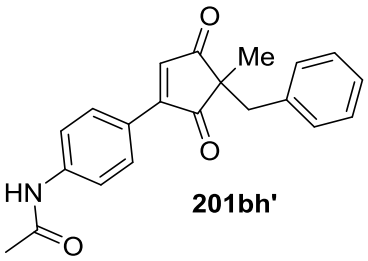
201bg'

4-Hydroxymethylphenyl boronic acid **6g'** (33.3 mg, 0.219 mmol, 2.2 equiv.) was heated (heat gun) under vacuum to convert it to the boroxine before a N_2 environment was introduced. 2-Benzyl-2-methylcyclopent-4-ene-1,3-dione **183b** (20.3 mg, 0.101 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.3 mg, 5.8 μmol, 0.06 equiv.) were added in order, with a N_2 environment being re-introduced after each addition. Anhydrous DMF (1 mL) was then added before the resulting solution was allowed to stir at 70 °C in an O_2 environment (balloon). Additional portions of 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.2 mg, 5.3 μmol, 0.053 equiv.) were added after 18 h, 21 h and 24 h and the reaction was left to stir at 70 °C under an O_2 atmosphere for a further 16 h. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc, 1:1) to yield **201bg'** (23.5 mg, 76.7 μmol, 76%) as a yellow oil.

R_f = 0.44 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 – 7.63 (m, 2H, Ar-H), 7.46 – 7.34 (m, 2H, Ar-H), 7.14 – 7.05 (m, 3H, Ar-H), 7.02 (s, 1H, =CH), 7.00 – 6.91 (m, 2H, Ar-H), 4.72 (s, 2H, CH_2), 3.05 (s, 2H, CH_2), 1.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.4 (C), 205.6 (C), 156.7 (C), 144.4 (C), 140.8 (CH), 135.7 (C), 129.6 (CH), 129.2 (CH), 128.3 (CH), 128.1 (C), 126.96 (CH), 126.95 (CH), 64.7 (CH_2), 53.9 (C), 41.6 (CH_2), 19.5 (CH_3); ν_{max}/cm^{-1} 3415 br w, 3029 w, 2926 w, 1739 w, 1691 v

str, 1604 w, 1585 m, 1562 w, 1451 w, 1205 w, 1047 m, 828 m, 753 m, 701 str; HRMS (NSI) *m/z calc*. for $C_{20}H_{19}O_3$: 307.1329 $[M+H]^+$; found: 307.1332.

_N_-(4-(4-benzyl-4-methyl-3,5-dioxocyclopent-1-en-1-yl)phenyl)acetamide (201bh')



201bh'

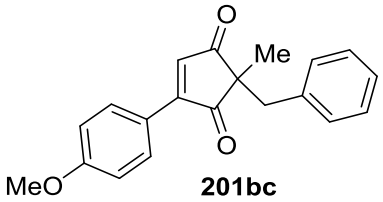
4-Acetamidophenyl boronic acid **6h'** (39.4 mg, 0.220 mmol, 2.2 equiv.) was heated (heat gun) under vacuum to convert it to the boroxine before a N_2 environment was introduced. 2-Benzyl-2-methylcyclopent-4-ene-1,3-dione **183b** 20.1 mg, 0.100 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.3 mg, 5.8 μmol, 0.06 equiv.) were added in order, with a N_2 environment being re-introduced after each addition. Anhydrous DMF (1 mL) was then added before the resulting solution was allowed to stir at 70 °C in an O_2 environment (balloon) for 28 h. The reaction was removed from the heat for further addition of 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.3 mg, 5.8 μmol, 0.058 equiv.) and left to stir at 70 °C under an O_2 atmosphere for a further 17 h. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane:EtOAc, gradient 5:1 to 1:3) to yield **201bh'** (28.3 mg, 84.8 μmol, 84%) as a yellow oil.

R_f = 0.31 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 – 7.63 (m, 3H, Ar-H and NH), 7.62 – 7.51 (m, 2H, Ar-H), 7.17 – 7.02 (m, 3H, Ar-H), 6.99 (s, 1H, =CH), 6.98 – 6.87 (m, 2H, Ar-H), 3.04 (s, 2H, CH_2Ph), 2.18 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.7 (C), 205.5 (C), 168.6 (C), 155.8 (C), 140.8 (C), 139.6 (CH), 135.7 (C), 130.1 (CH), 129.6 (CH), 128.2 (CH), 126.3 (CH), 124.4 (C), 119.4 (CH), 53.9 (C), 41.5 (CH_2), 24.7 (CH_3), 19.5 (CH_3); ν_{max}/cm^{-1} 3307 w, 2964 w, 1739 m, 1688 v str, 1662 str, 1592 str, 1507 v str, 1452 m, 1410 m, 1317 v str, 1258 v

str, 1184 m, 1051 m, 844 m, 753 v str, 700 v str; HRMS (NSI) *m/z calc*. for $C_{21}H_{20}NO_3$: 334.1438 $[M+H]^+$; found: 334.1442.

Enantioselective oxidative Heck reactions

2-Benzyl-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione (201bc)



201bc

Racemic procedure carried out by other members of the Lee Group.

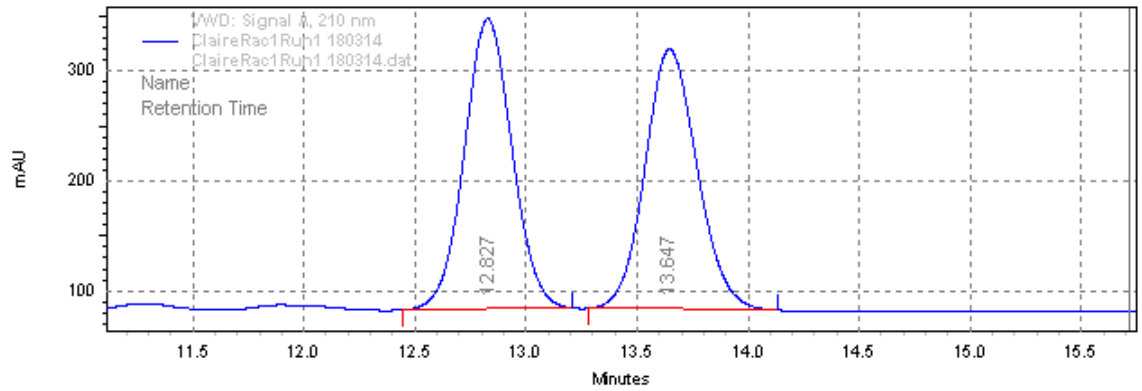
Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.3 mg, 11.3 μmol, 0.11 equiv.) was added to a dried flask which was subsequently purged with N_2. DMA (0.5 mL), followed by $Pd(OAc)_2$ (2.2 mg, 9.8 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Benzyl-2-methylcyclopent-4-ene-1,3-dione **183b** (20.6 mg, 0.103 mmol, 1 equiv.), was added to the solution followed by DMA (0.5 mL) and 4-methoxyphenyl boronic acid **6c** (32.5 mg, 0.24 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine, dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 20:1) to yield (*S*)-2-benzyl-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **201bc** (25.6 mg, 0.0836 mmol, 81%) as yellow crystals (65:35 er).

M.p. 89 - 91 °C; R_f = 0.36 (5:1 petroleum ether/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 9.0 Hz, 2H, Ar-H), 7.11 - 7.06 (m, 3H, Ar-H), 6.99 - 6.96 (m, 3H, Ar-H + =CH), 6.91 (d, J = 9.0 Hz, 2H, Ar-H), 3.84 (s, 3H, OCH_3), 3.04 (s, 2H, CH_2), 1.32 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 207.1 (C), 205.6 (C), 162.4 (C), 156.1 (C), 138.8 (CH), 136.0 (C), 131.1 (CH), 129.8 (CH), 128.3 (CH), 127.0 (CH), 121.5 (C), 114.4 (CH), 55.5 (CH_3), 54.0 (C), 41.6 (CH_2), 19.8 (CH_3); ν_{max}/cm^{-1} 3069, 2972, 2937,

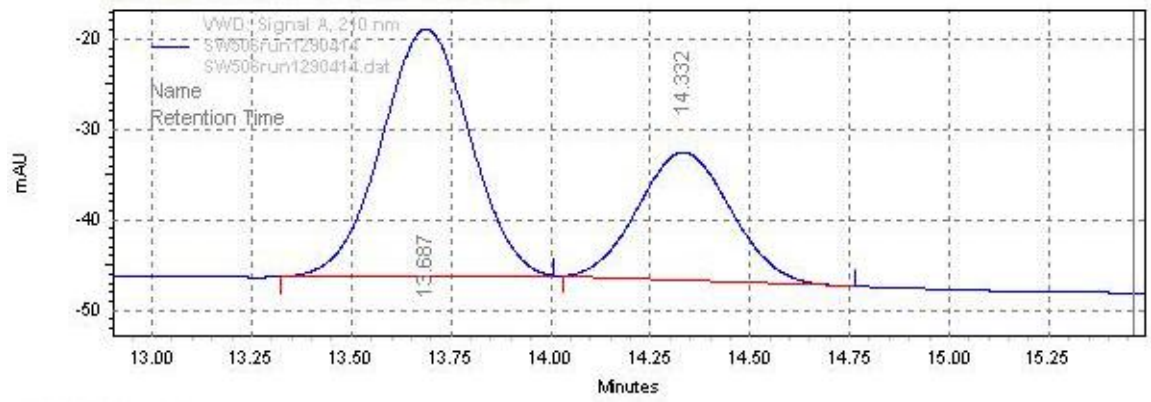
2846, 1731, 1712, 1684, 1604, 1585, 1563, 1509, 1453, 1422, 1372, 1267, 1181, 1025; HRMS (APCI) *m/z calc*. for $C_{20}H_{18}O_3H$: 307.1329 $[M+H]^+$; found: 307.1331.

$[\alpha]_D^{22}$ = +54.0 (*c* 1.00, $CHCl_3$); 65:35 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 13.7 min, t_R of minor isomer: 14.3 min.



VWD: Signal A, 210 nm Results

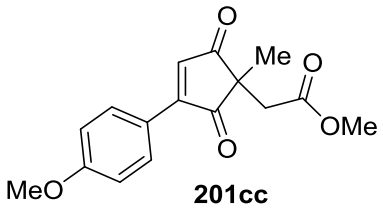
Retention Time	Area	Area %	Height	Height %
12.827	66241476	50.57	4423825	52.77
13.647	64742384	49.43	3959541	47.23



VWD: Signal A, 210 nm Results

Retention Time	Area	Area %	Height	Height %
13.687	7073473	64.88	458540	65.91
14.332	3828251	35.12	237121	34.09

Methyl-2-(3-(4-methoxyphenyl)-1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate (201cc)



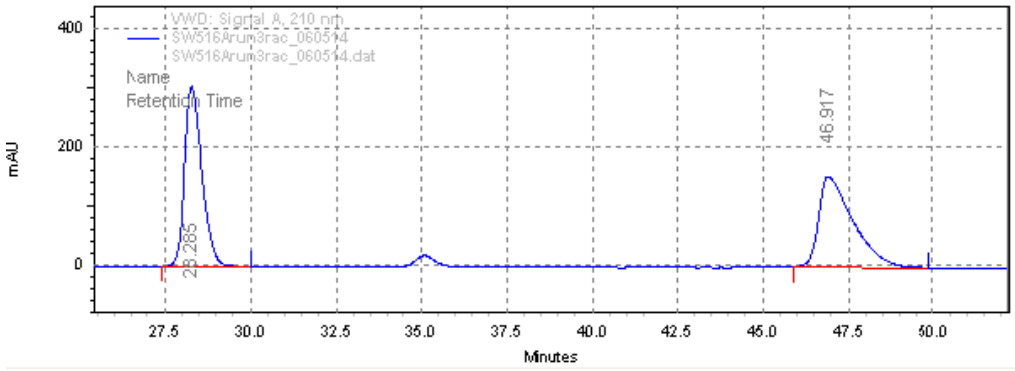
201cc

Racemic procedure carried out by Claire Lamb.

Enantioselective procedure (Table 31, Entry 3):

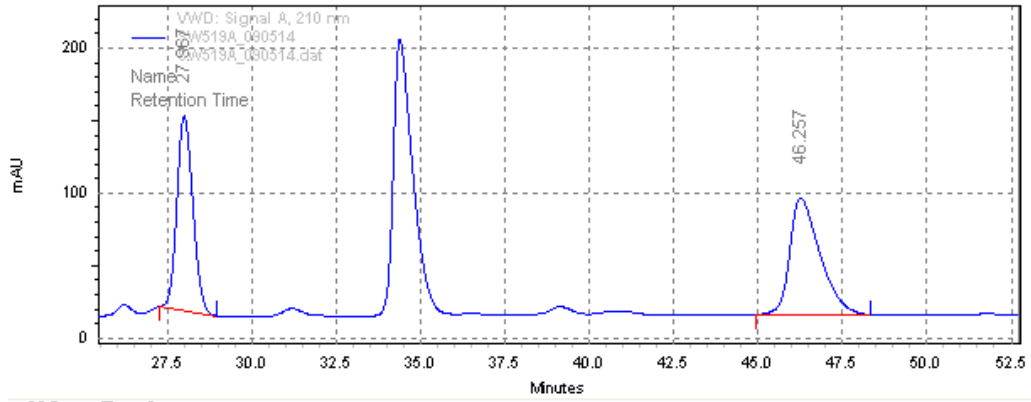
4-Methoxyphenyl boronic acid **6c** (36.5 mg, 0.24 mmol, 2.4 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. Methyl 2-(1-methyl-2,5-dioxocyclopent-3-en-1-yl)acetate **183c** (18.2 mg, 0.0999 mmol, 1 equiv.), (*S*)-4-*tert*-Butyl-2-(2-pyridyl)oxazoline **210** (1.2 mg, 5.9 μmol, 0.06 equiv.) and $Pd(OAc)_2$ (1.2 mg, 5.3 μmol, 0.05 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (1 mL) was added and the reaction was left to stir at 70 °C under an O_2 atmosphere (balloon). After 24 h, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude mixture was used for chiral HPLC analysis (using a racemic sample synthesised by C. Lamb for reference) and an enantiomeric ratio of 47:53 was obtained.

47:53 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 46.3 min, t_R of minor isomer: 28.0 min.



VWD: Signal A, 210 nm Results

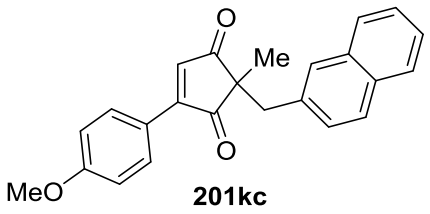
Retention Time	Area	Area %	Height	Height %
28.285	178665450	49.96	5114996	66.48
46.917	178984335	50.04	2579047	33.52



210 nm Results

Retention Time	Area	Area %	Height	Height %
27.967	73776806	46.64	2250728	62.45
46.257	84418983	53.36	1353074	37.55

4-(4-Methoxyphenyl)-2-methyl-2-(naphthalen-2-ylmethyl)cyclopent-4-ene-1,3-dione (201kc)



201kc

Racemic procedure carried out by Claire Lamb.

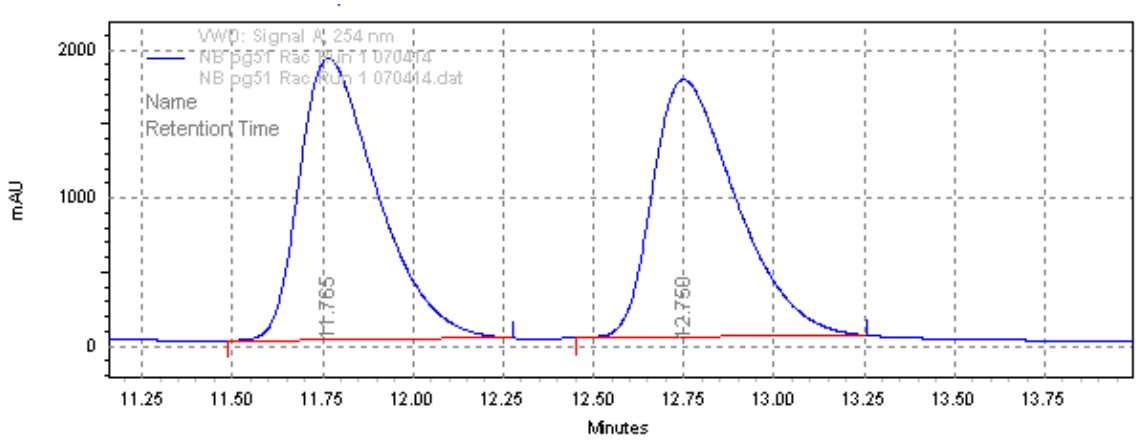
Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.4 mg, 11.8 μmol, 0.12 equiv.) was added to a dried flask which was subsequently purged with N_2. DMA (0.4 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.3 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(naphthalen-2-ylmethyl)cyclopent-4-ene-1,3-dione **183k** (25.0 mg, 0.0998 mmol, 1 equiv.), was added to the solution followed by DMA (0.6 mL) and 4-methoxyphenyl boronic acid **6c** (32.1 mg, 0.24 mmol, 2.5 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine, dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 20:1→10:1) to yield (*S*)-4-(4-methoxyphenyl)-2-methyl-2-(naphthalen-2-ylmethyl)cyclopent-4-ene-1,3-dione **201kc** (25.1 mg, 0.0704 mmol, 71%) as a yellow solid (62:38 er).

M.p. 91-95 °C; R_f = 0.31 (5:1 petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 – 7.63 (m, 4H, Ar-H), 7.58 (d, J = 8.4 Hz, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.39 – 7.33 (m, 2H, Ar-H), 7.10 (dd, J = 8.4, 1.7 Hz, 1H, Ar-H), 6.92 (s, 1H, C=CH), 6.86 (d, J = 9.0 Hz, 2H, Ar-H), 3.81 (s, 3H, OCH_3), 3.21 (s, 2H, CH_2), 1.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.0 (C), 205.4 (C), 162.2 (C), 156.0 (C), 138.7 (CH), 133.5 (C), 133.2 (C), 132.3 (C), 131.0 (CH), 128.6 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 125.9 (CH), 125.6 (CH), 121.4 (C), 114.3 (CH), 55.4 (CH_3), 54.0 (C), 41.4 (CH_2), 20.0 (CH_3); ν_{max}/cm^{-1} 2928, 2842, 1736, 1690, 1603, 1583, 1564,

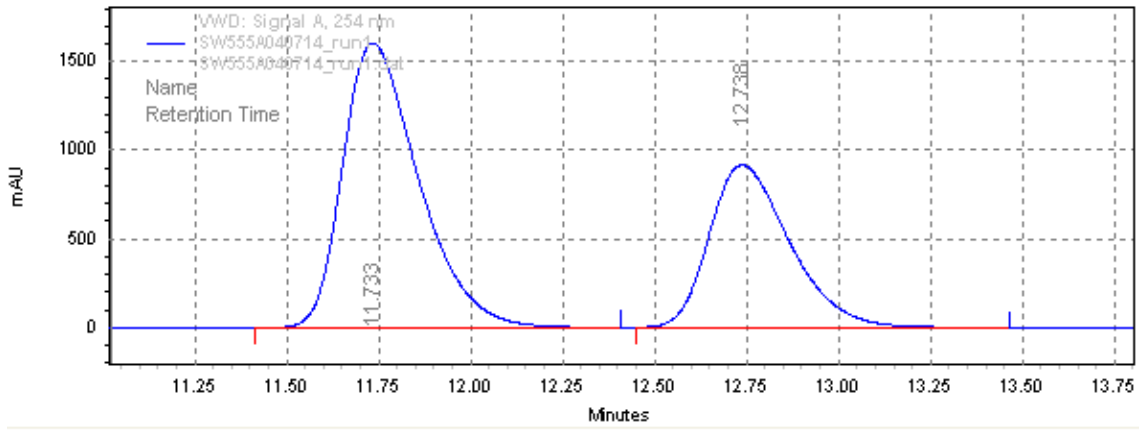
1506, 1453, 1371, 1325, 1309, 1294, 1257, 1178, 1109, 1052, 1027, 897, 864, 836, 822, 750; HRMS (ESI) *m/z calc*. for $C_{24}H_{21}O_3$: 357.1485 $[M+H]^+$; found: 357.1482.

$[\alpha]_D^{24}$ = +62.0 (*c* 1.00, $CHCl_3$); 62:38 er; HPLC (CHIRALPAK IB, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 11.7 min, t_R of minor isomer: 12.7 min.



VWD: Signal A, 254 nm Results

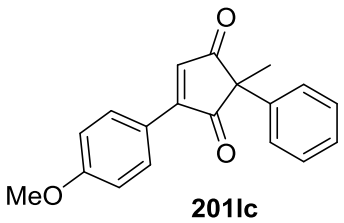
Retention Time	Area	Area %	Height	Height %
11.765	478854765	50.45	31941147	52.25
12.750	470345466	49.55	29193743	47.75



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
11.733	386710843	62.30	26929206	63.65
12.738	233976227	37.70	15377848	36.35

4-(4-Methoxyphenyl)-2-methyl-2-phenylcyclopentene-1,3-dione (201lc)



201lc

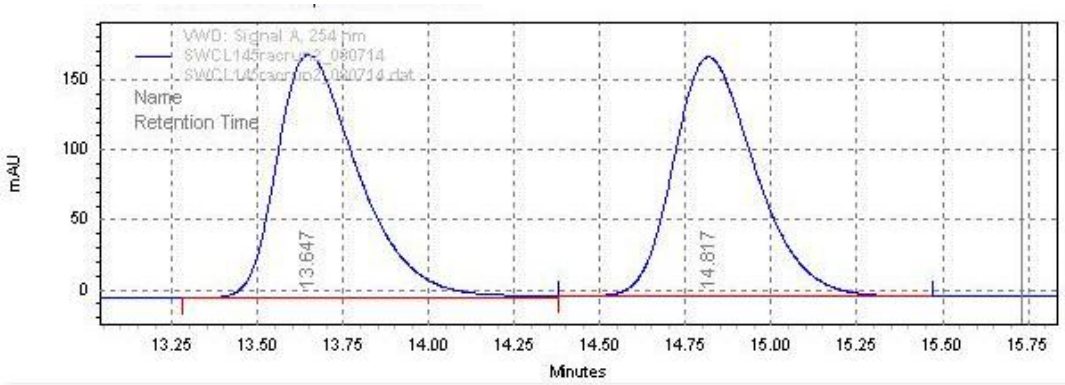
Racemic procedure carried out by Claire Lamb, MChem project student.

Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.3 mg, 11.3 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.4 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-phenylcyclopentene-1,3-dione **183l** (18.8 mg, 0.101 mmol, 1 equiv.), was added to the solution followed by DMA (0.6 mL) and 4-methoxyphenyl boronic acid **6c** (32.4 mg, 0.24 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 20:1→15:1) to yield (*S*)-4-(4-methoxyphenyl)-2-methyl-2-phenylcyclopentene-1,3-dione **201lc** (27.5 mg, 0.094 mmol, 93%) as a yellow oil (83:17 er).

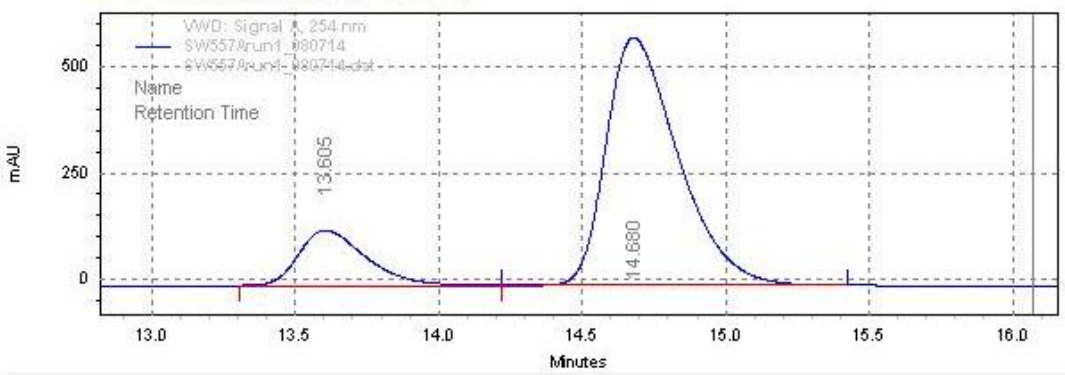
M.p. 105-106 °C; R_f = 0.1 (10:1 petrol ether:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.31 – 7.13 (m, 6H, Ar-H and alkene-H), 6.91 (d, *J* = 9.1 Hz, 2H, Ar-H), 3.79 (s, 3H, OCH_3), 1.56 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 204.6 (C), 203.3 (C), 162.6 (C), 155.5 (C), 137.9 (CH), 137.7 (C), 131.3 (CH), 128.8 (CH), 127.6 (CH), 126.4 (CH), 121.5 (C), 114.5 (CH), 56.1 (C), 55.5 (CH_3), 19.9 (CH_3); ν_{max}/cm^{-1} 2969, 1736, 1695, 1603, 1508, 1444, 1257, 1180, 1046, 837, 698; HRMS (APCI) *m/z* calc. for $C_{19}H_{17}O_3$: 293.1177 $[M+H]^+$; found: 293.1178.

$[\alpha]_D^{28}$ = +77.8 (*c* 0.18, $CHCl_3$); 83:17 er; HPLC (CHIRALPAK IB, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 254 nm) t_R of major isomer: 14.7 min, t_R of minor isomer: 13.6 min.



VWD: Signal A, 254 nm Results

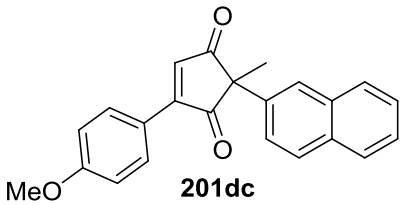
Retention Time	Area	Area %	Height	Height %
13.647	48356060	50.06	2915702	50.37
14.817	48235074	49.94	2873310	49.63



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
13.605	35338979	17.20	2170867	18.22
14.680	170095100	82.80	9742169	81.78

4-(4-Methoxyphenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione (201dc)



201dc

Racemic procedure:

4-Methoxyphenyl boronic acid **6c** (36.3 mg, 0.24 mmol, 2.4 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 2-Methyl-2-(naphthalen-2-yl)cyclopentane-1,3-dione (23.6 mg, 0.10 mmol, 1 equiv.) **183d**, 1,10-phenanthroline **44** (1.0 mg, 5.6 μmol, 0.056 equiv.) and $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.049 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (1 mL) was added and the reaction was left to stir at 70 °C for 70 h under an O_2 atmosphere (balloon). On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 20:1→10:1) to yield 4-(4-methoxyphenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201dc** (31.1 mg, 0.091 mmol, 91%) as a yellow crystalline solid.

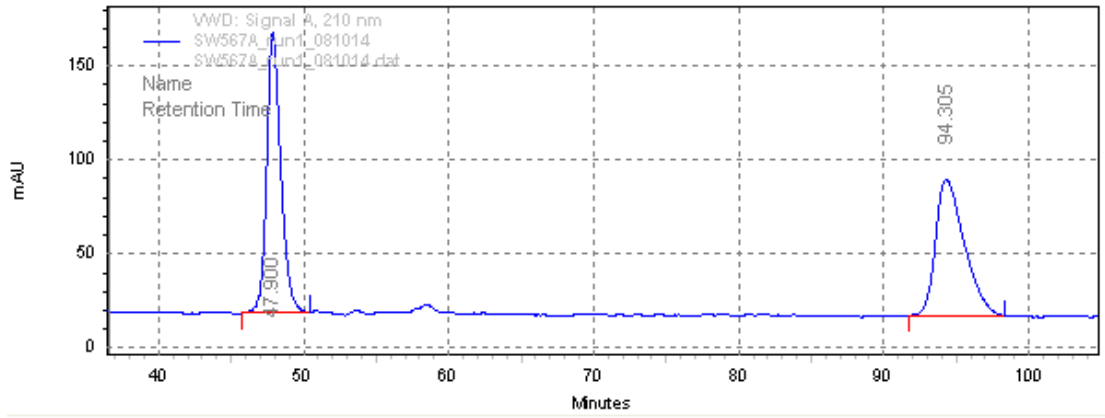
M.p. 144-146 °C; R_f = 0.38 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, J = 9.0 Hz, 2H, Ar-H), 7.87 – 7.73 (m, 4H, Ar-H), 7.55 – 7.42 (m, 3H, Ar-H), 7.39 (s, 1H, alkene-H), 7.00 (d, J = 9.0 Hz, 2H, Ar-H), 3.87 (s, 3H, OCH_3), 1.75 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.5 (C), 203.2 (C), 162.6 (C), 155.4 (C), 137.9 (CH), 135.1 (C), 133.2 (C), 132.5 (C), 131.4 (CH), 128.6 (CH), 128.1 (CH), 127.5 (CH), 126.29 (CH), 126.26 (CH), 125.7 (CH), 124.1 (CH), 121.5 (C), 114.6 (CH), 56.3 (C), 55.5 (CH_3), 20.0 (CH_3); ν_{max}/cm^{-1} 3057 w, 2997 w, 1733 w, 1683 v str, 1599 m, 1580 v str, 1506 str, 1457 m, 1435 w, 1329 m, 1312 m, 1239 str, 1185 str, 1099 m, 1045 m, 902 m, 881 w, 838 v str, 824 v str; HRMS (APCI) *m/z* calc. for $C_{23}H_{19}O_3$: 343.1329 $[M+H]^+$; found: 343.1330.

Enantioselective procedure:

(*S*)-4-(*Tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** (3.0 mg, 11.0 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.4 mL), followed by $Pd(OAc)_2$ (2.4 mg, 10.7 μmol, 0.11 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.7 mg, 0.1003 mmol, 1 equiv.), was added to the solution followed by DMA (0.6 mL) and 4-methoxyphenyl boronic acid **6c** (32.6 mg, 0.244 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 25:1) to yield (*S*)-4-(4-methoxyphenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201dc** (34.2 mg, 0.100 mmol, 100%) as a yellow solid (90:10 er).

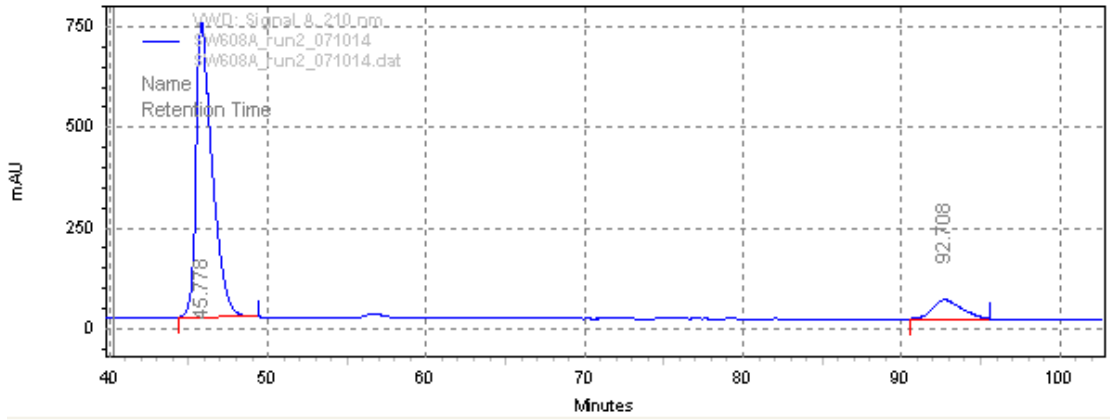
See racemic procedure above for characterisation.

$[\alpha]_D^{25}$ = +133.3 (*c* 0.12, $CHCl_3$); 90:10 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 45.8 min, t_R of minor isomer: 92.7 min.



VWD: Signal A,
210 nm Results

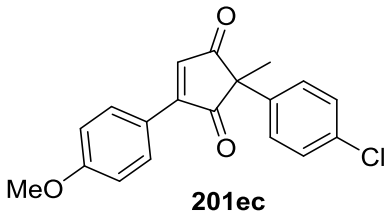
Retention Time	Area	Area %	Height	Height %
47.900	168392572	50.15	2503773	67.42
94.305	167386735	49.85	1210129	32.58



VWD: Signal A,
210 nm Results

Retention Time	Area	Area %	Height	Height %
45.778	890351112	89.73	12340211	93.89
92.708	101864324	10.27	802627	6.11

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione (201ec)



201ec

Racemic procedure:

4-Methoxyphenyl boronic acid **6c** (18.2 mg, 0.120 mmol, 2.4 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 2-(4-Chlorophenyl)-2-methylcyclopent-4-ene-1,3-dione **183e** (11.0 mg, 0.0499 mmol, 1 equiv.), 1,10-phenanthroline **44** (0.6 mg, 3.3 μmol, 0.067 equiv.) and $Pd(OAc)_2$ (0.6 mg, 2.7 μmol, 0.054 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (0.5 mL) was added, the reaction was left to stir at 70 °C for 70 h under an O_2 atmosphere (balloon). On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc gradient 10:1) to yield 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **201ec** (15.5 mg, 0.0474 mmol, 95%) as a yellow oil.

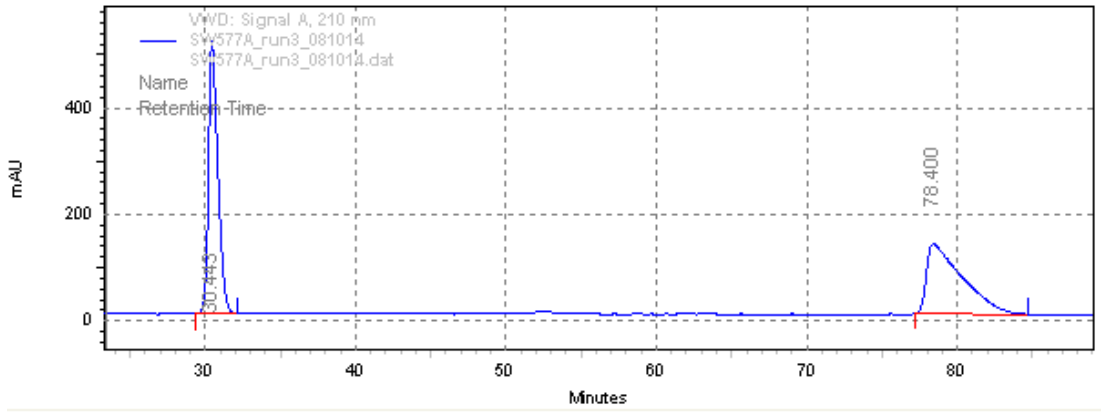
R_f = 0.13 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.9 Hz, 2H, Ar-H), 7.34 – 7.19 (m, 5H, Ar-H and alkene-H), 6.96 (d, J = 8.9 Hz, 2H, Ar-H), 3.84 (s, 3H, CH_3), 1.58 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.3 (C), 202.9 (C), 162.8 (C), 155.4 (C), 137.8 (CH), 136.2 (C), 133.7 (C), 131.4 (CH), 128.9 (CH), 128.0 (CH), 121.4 (C), 114.6 (CH), 55.5 (C and CH_3), 20.3 (CH_3); ν_{max}/cm^{-1} 2933 w, 2839 w, 1737 w, 1689 v str, 1601 str, 1575 str, 1506 v str, 1492 str, 1253 v str, 1177 v str, 1095 str, 1046 str, 1026 str, 836 str, 808 str; HRMS (NSI) *m/z* calc. for $C_{19}H_{16}O_3Cl$: 327.0782 $[M+H]^+$; found: 327.0786.

Enantioselective procedure:

(*S*)-4-(*Tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **210** (3.0 mg, 11.0 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.4 mL), followed by $Pd(OAc)_2$ (2.4 mg, 10.7 μmol, 0.11 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-(4-Chlorophenyl)-2-methylcyclopent-4-ene-1,3-dione **183e** (22.0 mg, 0.0997 mmol, 1 equiv.), was added to the solution followed by DMA (0.6 mL) and 4-methoxyphenyl boronic acid **6c** (32.3 mg, 0.241 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 10:1) to yield (*S*)-2-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **201ec** (29.2 mg, 0.0893 mmol, 90%) as a yellow oil (80:20 er).

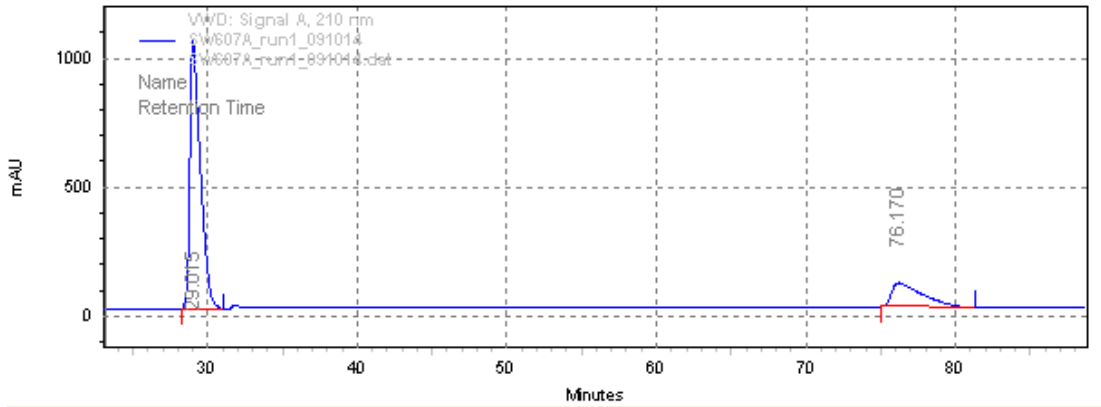
See racemic procedure above for characterisation.

$[\alpha]_D^{25}$ = +86.0 (*c* 1.00, $CHCl_3$); 80:20 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 29.0 min, t_R of minor isomer: 76.2 min.



VWD: Signal A,
210 nm Results

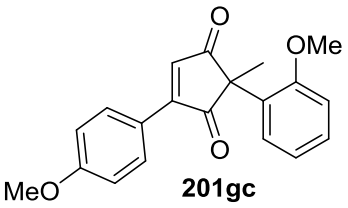
Retention Time	Area	Area %	Height	Height %
30.443	368036250	50.28	8602387	79.68
78.400	363906806	49.72	2194144	20.32



VWD: Signal A,
210 nm Results

Retention Time	Area	Area %	Height	Height %
29.015	847120840	79.82	17456077	91.91
76.170	214234541	20.18	1536984	8.09

2-(2-Methoxyphenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione (201gc)



201gc

Racemic procedure:

4-Methoxyphenyl boronic acid **6c** (18.3 mg, 0.120 mmol, 2.4 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 2-(2-Methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **183g** (10.9 mg, 0.0504 mmol, 1 equiv.), 1,10-phenanthroline **44** (0.6 mg, 3.3 μmol, 0.058 equiv.) and $Pd(OAc)_2$ (0.6 mg, 2.7 μmol, 0.053 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (0.5 mL) was added, the reaction was left to stir at 70 °C for 70 h under an O_2 atmosphere (balloon). On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 20:1→5:1) to yield 2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **201gc** (14.5 mg, 0.0450 mmol, 89%) as a yellow oil.

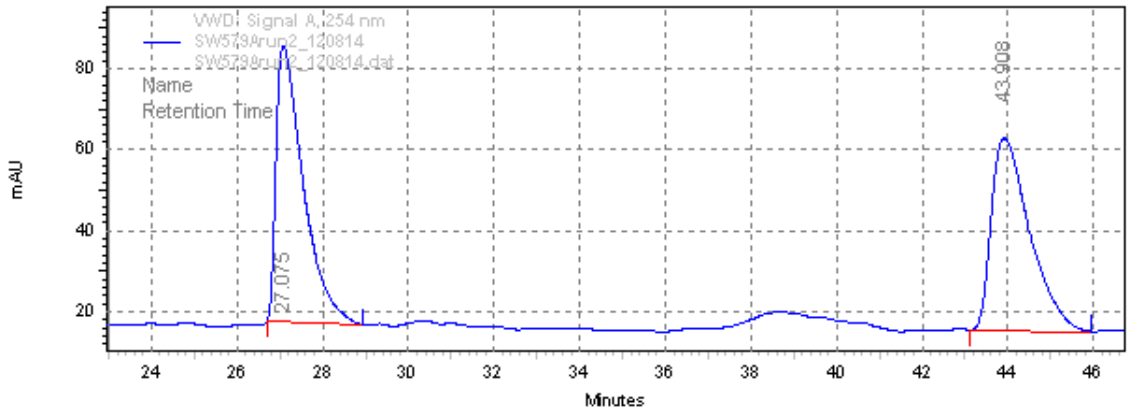
R_f = 0.31 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 9.0 Hz, 2H, Ar-H), 7.41 (dd, J = 7.7, 1.6 Hz, 1H, Ar-H), 7.31 – 7.26 (m, 1H, Ar-H), 7.20 (s, 1H, alkene-H), 7.07 – 7.02 (m, 1H, Ar-H), 7.01 (d, J = 9.0 Hz, 2H, Ar-H), 6.77 (dd, J = 8.2, 1.1 Hz, 1H, Ar-H), 3.88 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 1.63 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.1 (C), 205.3 (C), 162.2 (C), 156.2 (C), 153.0 (C), 134.9 (CH), 131.0 (CH), 129.3 (CH), 129.1 (CH), 126.2 (C), 122.2 (C), 121.3 (CH), 114.5 (CH), 110.9 (CH), 55.4 (CH_3), 55.3 (CH_3), 54.8 (C), 19.4 (CH_3); ν_{max}/cm^{-1} 2978 w, 2939 w, 1733 w, 1687 v str, 1601 str, 1585 str, 1508 str, 1491 str, 1251 v str, 1176 v str, 1040 m, 1014 str, 835 str, 773 str; HRMS (NSI) *m/z* calc. for $C_{20}H_{19}O_4$: 323.1278 $[M+H]^+$; found: 323.1276.

Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.2 mg, 10.8 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.8 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-(2-Methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **183g** (21.4 mg, 0.0990 mmol, 1 equiv.), was added to the solution followed by DMA (0.2 mL) and 4-methoxyphenyl boronic acid **6c** (32.8 mg, 0.245 mmol, 2.5 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 15:1→7:1) to yield (*S*)-2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **201gc** (27.1 mg, 0.0841 mmol, 85%) as a yellow oil (78:22) er.

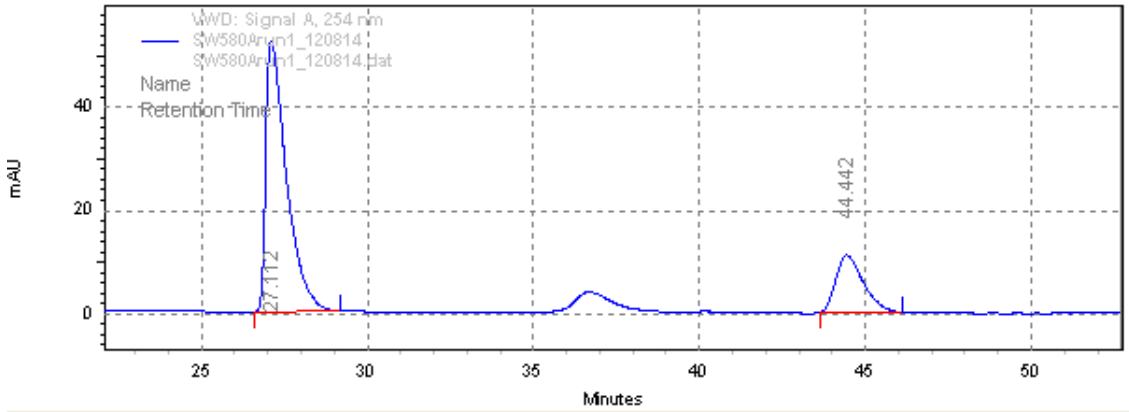
See racemic procedure for characterisation.

$[\alpha]_D^{24}$ = -56.0 (*c* 1.00, $CHCl_3$); 78:22 er; HPLC (CHIRALPAK IB, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 27.1 min, t_R of minor isomer: 44.4 min.



VWD: Signal A,
254 nm Results

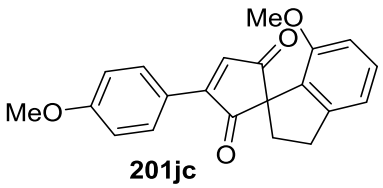
Retention Time	Area	Area %	Height	Height %
27.075	50347435	50.21	1139289	58.92
43.908	49926816	49.79	794298	41.08



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
27.112	38264978	78.31	882509	82.65
44.442	10596134	21.69	185305	17.35

7'-Methoxy-3-(4-methoxyphenyl)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione (201jc)



201jc

4-Methoxyphenyl boronic acid **6c** (18.2 mg, 0.120 mmol, 2.4 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 7'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione **183j** (11.5 mg, 0.0504 mmol, 1 equiv.), 1,10-phenanthroline **44** (0.6 mg, 3.3 μmol, 0.066 equiv.) and $Pd(OAc)_2$ (0.6 mg, 2.7 μmol, 0.053 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (0.5 mL) was added and the reaction was left to stir at 70 °C for 70 h under an O_2 atmosphere (balloon). On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 15:1→7:1) to yield 7'-methoxy-3-(4-methoxyphenyl)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione **201jc** (13.8 mg, 0.0413 mmol, 82%) as a yellow solid.

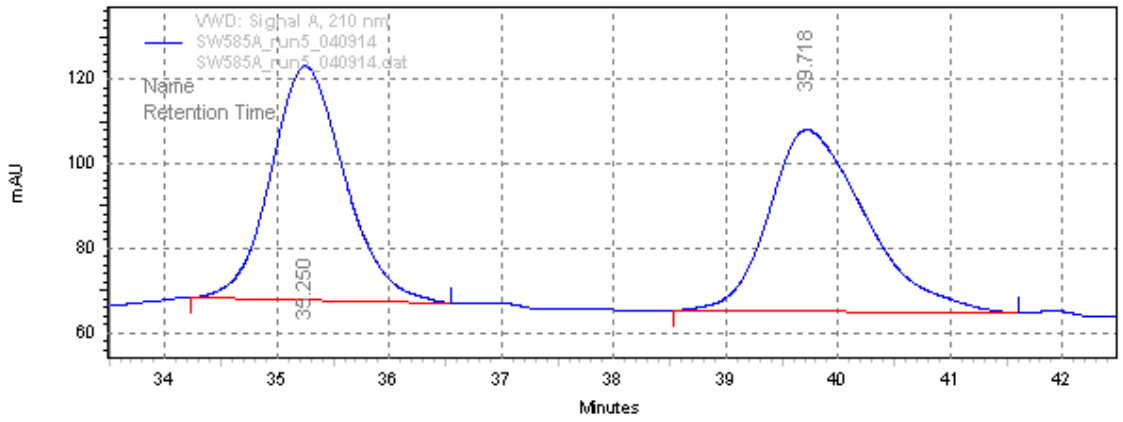
M. p. 147-149 °C; R_f = 0.31 (1:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.31 (s, 1H, alkene-H), 7.21 (dd, *J* = 8.2, 7.6 Hz, 1H, Ar-H), 7.01 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.91 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar-H), 6.59 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar-H), 3.88 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.35 – 3.08 (m, 2H, CH_2), 2.49 – 2.29 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.5 (C), 204.4 (C), 162.2 (C), 155.5 (C), 155.2 (C), 148.2 (C), 137.7 (CH), 131.1 (CH), 130.2 (CH), 128.3 (C), 122.2 (C), 117.4 (CH), 114.5 (CH), 108.5 (CH), 62.9 (C), 55.4 (CH_3), 55.3 (CH_3), 34.4 (CH_2), 32.3 (CH_2); ν_{max}/cm^{-1} 2933 w, 2843 w, 1737 m, 1686 v str, 1601 m, 1580 v str, 1506 m, 1262 v str, 1202 m, 1178 m, 1078 m, 778 str; HRMS (NSI) *m/z* calc. for $C_{21}H_{19}O_4$: 335.1278 $[M+H]^+$; found: 335.1281.

Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.3 mg, 11.3 μmol, 0.12 equiv.) was added to a dried flask, purged with N_2. DMA (0.8 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.11 equiv.) were added and the solution was left to stir at room temperature for 1 h. 7'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione **183j** (22.2 mg, 0..0973 mmol, 1 equiv.), was added to the solution followed by DMA (0.2 mL) and 4-methoxyphenyl boronic acid **6c** (32.8 mg, 0.245 mmol, 2.5 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 10:1→7:1) to yield 7'-methoxy-3-(4-methoxyphenyl)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione **201jc** (27.7 mg, 0.0828 mmol, 85%) as a yellow solid (45:55 er).

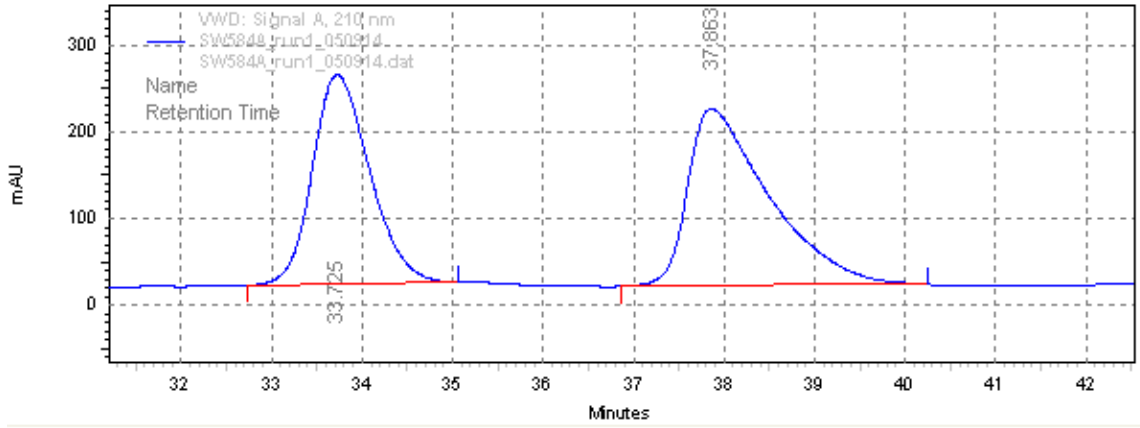
See racemic procedure for characterisation.

$[\alpha]_D^{24}$ = +0.06 (*c* 1.00, $CHCl_3$); 55:45 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 37.9 min, t_R of minor isomer: 33.7 min.



VWD: Signal A,
210 nm Results

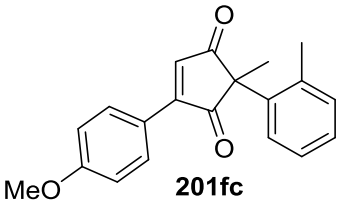
Retention Time	Area	Area %	Height	Height %
35.250	42191940	49.34	927646	56.27
39.718	43318370	50.66	721047	43.73



VWD: Signal A,
210 nm Results

Retention Time	Area	Area %	Height	Height %
33.725	178252979	45.48	4045102	54.15
37.863	213662785	54.52	3424440	45.85

4-(4-Methoxyphenyl)-2-methyl-2-(*o*-tolyl)cyclopent-4-ene-1,3-dione (201fc)



201fc

Racemic procedure:

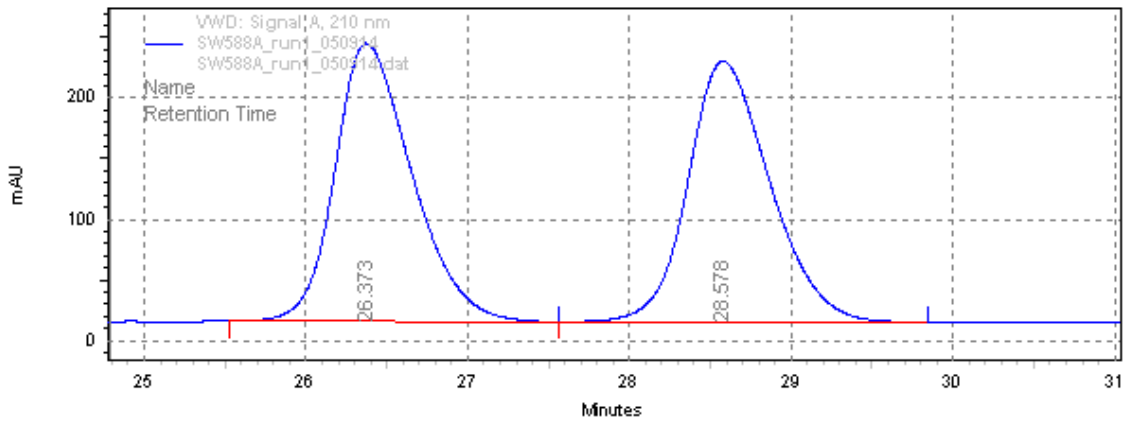
4-Methoxyphenyl boronic acid **6c** (18.2 mg, 0.120 mmol, 2.4 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 2-Methyl-2-(*o*-tolyl)cyclopent-4-ene-1,3-dione **183f** (10.0 mg, 0.0499 mmol, 1 equiv.), 1,10-phenanthroline **44** (0.6 mg, 3.3 μmol, 0.067 equiv.) and $Pd(OAc)_2$ (0.6 mg, 2.7 μmol, 0.054 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (0.5 mL) was added and the reaction was left to stir at 70 °C for 70 h under an O_2 atmosphere (balloon). On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 10:1→5:1) to yield 4-(4-Methoxyphenyl)-2-methyl-2-(*o*-tolyl)cyclopent-4-ene-1,3-dione **(201fc)** (8.2 mg, 0.0268 mmol, 54%) as a yellow oil.

R_f = 0.71 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 9.1 Hz, 2 H), 7.44 (dd, J = 7.8, 1.5 Hz, 1H, Ar-H), 7.30 (s, 1H, alkene H), 7.30 – 7.16 (m, 2H, Ar-H), 7.11 – 7.06 (m, 1H, Ar-H), 7.02 (d, J = 9.1 Hz, 2H, Ar-H), 3.89 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.75 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.0 (C), 204.6 (C), 162.6 (C), 153.5 (C), 136.1 (C), 135.9 (CH), 135.0 (C), 131.6 (CH), 131.3 (CH), 128.9 (CH), 128.2 (CH), 126.4 (CH), 121.6 (C), 114.6 (CH), 57.8 (C), 55.5 (CH_3), 22.1 (CH_3), 22.0 (CH_3); ν_{max}/cm^{-1} 2967 w, 2839 w, 1739 w, 1693 v str, 1601 v str, 1507 v str, 1459 w, 1424 w, 1255 v str, 1176 v str, 1088 m, 1046 m, 1022 m, 836 str, 747 v str; HRMS (NSI) *m/z* calc. for $C_{20}H_{19}O_3$: 307.1329 $[M+H]^+$; found: 307.1331.

Enantioselective procedure:

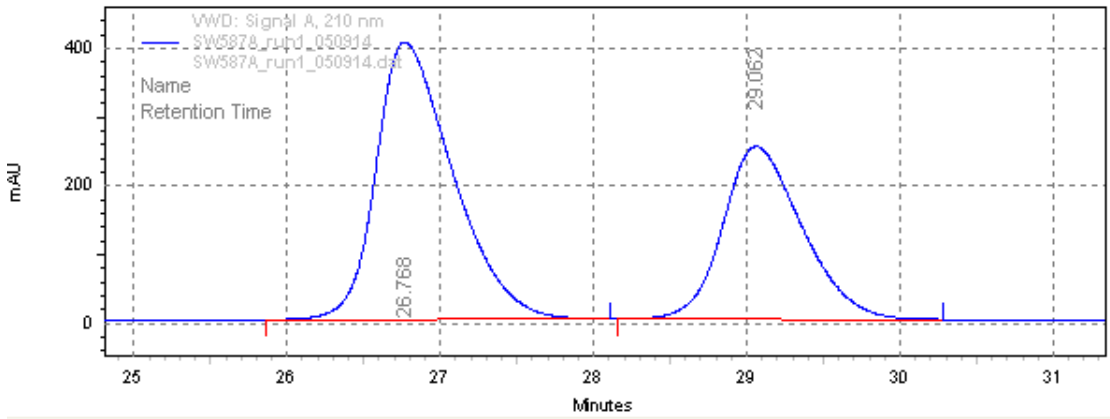
(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.3 mg, 11.3 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.8 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(*o*-tolyl)cyclopent-4-ene-1,3-dione **183f** (20.0 mg, 0.0999 mmol, 1 equiv.), was added to the solution followed by DMA (0.2 mL) and 4-methoxyphenyl boronic acid **6c** (32.7 mg, 0.244 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 10:1). A pure sample of product **201fc** unfortunately could not be isolated due to coelution with an impurity yet the impure sample was sufficient to use for HPLC analysis to give an indication of er (61:39 er).

61:39 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 95/5, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 26.8 min, t_R of minor isomer: 29.1 min.



VWD: Signal A, 210 nm Results

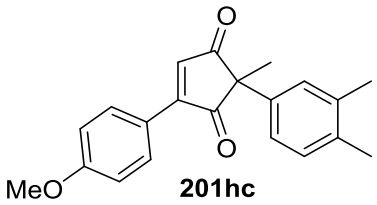
Retention Time	Area	Area %	Height	Height %
26.373	127757067	50.04	3851762	51.60
28.578	127561489	49.96	3612746	48.40



VWD: Signal A, 210 nm Results

Retention Time	Area	Area %	Height	Height %
26.768	235949218	60.87	6762168	61.60
29.062	151652396	39.13	4215696	38.40

2-(3,4-Dimethylphenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione (201hc)



201hc

Racemic procedure:

4-Methoxyphenyl boronic acid **6c** (36.7 mg, 0.242 mmol, 2.4 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 2-(3,4-Dimethylphenyl)-2-methylcyclopent-4-ene-1,3-dione **183h** (21.3 mg, 0.0994 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.067 equiv.) and $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.049 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (1.0 mL) was added and the reaction was left to stir at 70 °C for 70 h under an O_2 atmosphere (balloon). On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc gradient 15:1) to yield 2-(3,4-dimethylphenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **201hc** (29.0 mg, 0.0905 mmol, 91%) as a yellow oil.

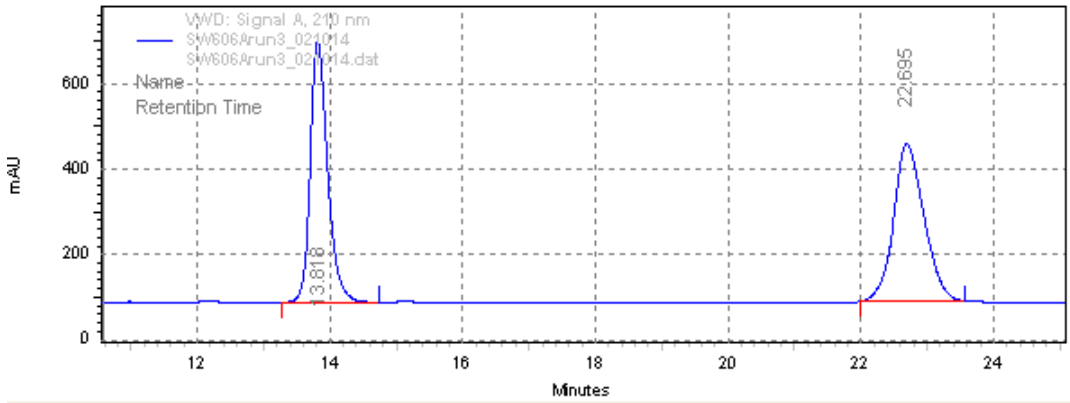
R_f = 0.31 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.9 Hz, 2H, Ar-H), 7.34 (s, 1H, alkene-H), 7.12 – 7.05 (m, 3H, Ar-H), 6.99 (d, J = 8.9 Hz, 2H, Ar-H), 3.88 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 1.62 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.8 (C), 203.6 (C), 162.5 (C), 155.4 (C), 137.9 (CH), 137.0 (C), 136.1 (C), 135.2 (C), 131.3 (CH), 130.0 (CH), 127.5 (CH), 123.8 (CH), 121.6 (C), 114.5 (CH), 55.9 (C), 55.4 (CH_3), 19.9 (CH_3), 19.6 (CH_3), 19.3 (CH_3); ν_{max}-/cm^{-1} 2925 w, 2838 w, 1731 m, 1680 v str, 1601 m, 1577 v str, 1505 m, 1238 v str, 1185 v str, 1103 m, 1049 m, 847 m; HRMS (NSI) *m/z* calc. for $C_{21}H_{21}O_3$: 321.1485 $[M+H]^+$; found: 321.1491.

Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.4 mg, 11.8 μmol, 0.12 equiv.) was added to a dried flask, purged with N_2. DMA (0.8 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-(3,4-Dimethylphenyl)-2-methylcyclopent-4-ene-1,3-dione **183h** (21.4 mg, 0.0999 mmol, 1 equiv.), was added to the solution followed by DMA (0.2 mL) and 4-methoxyphenyl boronic acid **6c** (32.1 mg, 0.240 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 15:1) to yield (*S*)-2-(3,4-dimethylphenyl)-4-(4-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **201hc** (32.0 mg, 0.0999 mmol, 100%) as a yellow oil (80:20 er).

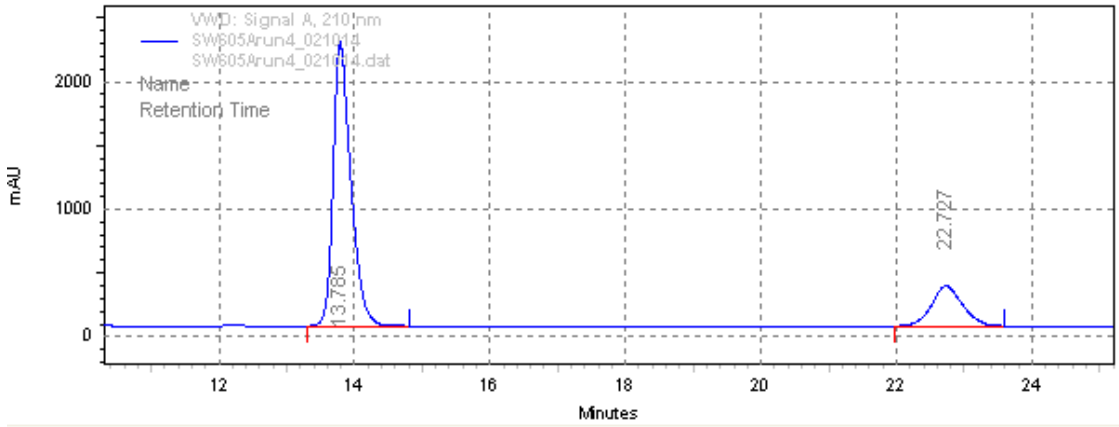
See racemic procedure for characterisation.

$[\alpha]_D^{24}$ = +122.0 (*c* 1.00, $CHCl_3$); 80:20 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 95/5, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 13.8 min, t_R of minor isomer: 22.7 min.



VWD: Signal A, 210 nm Results

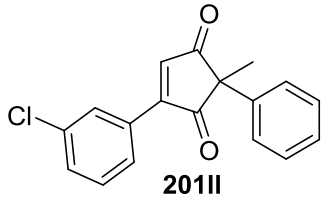
Retention Time	Area	Area %	Height	Height %
13.818	186581899	48.74	10293325	62.43
22.695	196229670	51.26	6195540	37.57



VWD: Signal A, 210 nm Results

Retention Time	Area	Area %	Height	Height %
13.785	685046108	80.37	37299761	87.64
22.727	167308107	19.63	5260784	12.36

4-(3-Chlorophenyl)-2-methyl-2-phenylcyclopent-4-ene-1,3-dione (201ll)



201ll

Racemic procedure:

3-(Chloro)phenylboronic acid **6l** (34.6 mg, 0.221 mmol, 2.2 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 2-Methyl-2-phenylcyclopentene-1,3-dione **183l** (18.6 mg, 0.099 mmol, 1 equiv.) and DMF (0.4 mL) were added, followed by 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.067 equiv.) and $Pd(OAc)_2$ (1.2 mg, 5.3 μmol, 0.054 equiv.), with an N_2 environment being reintroduced after each addition. DMF (0.6 mL) was added and the reaction was left to stir at 70 °C. After 24 h, an additional portion of ligand **44** (1.2 mg, 0.007 mmol, 0.07 equiv.) and catalyst (1.2 mg, 0.0053 mmol, 0.053 equiv.) were added and the reaction left to stir for a further 48 h under O_2 atmosphere (balloon). On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting crude was purified by silica gel column chromatography (25:1 hexane:EtOAc) to obtain 4-(3-Chlorophenyl)-2-methyl-2-phenylcyclopent-4-ene-1,3-dione **201ll** (21.0 mg, 0.071 mmol, 71%) as a yellow oil.

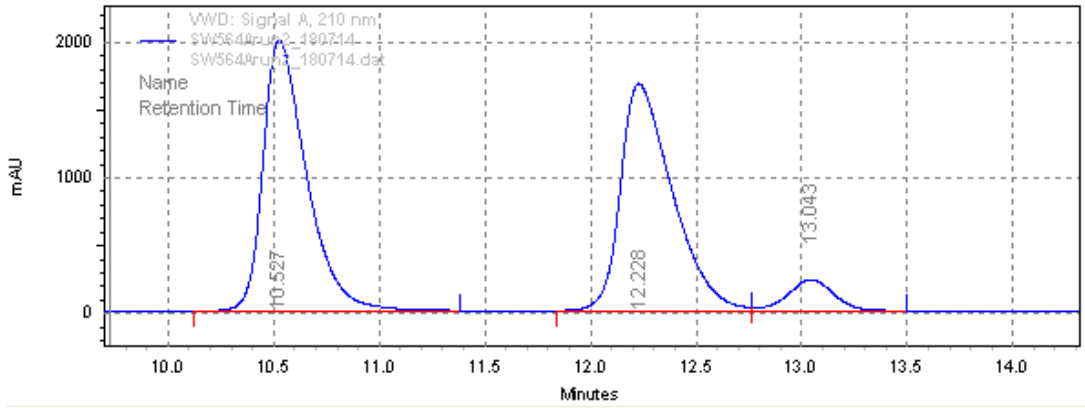
R_f = 0.75 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (1 H, t, J = 1.8 Hz, Ar-H), 7.79 – 7.74 (1 H, m, Ar-H), 7.45 – 7.16 (8 H, m, Ar-H and =CH), 1.58 (3 H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.5 (C), 203.1 (C), 154.8 (C), 141.1 (CH), 137.2 (C), 135.1 (C), 131.7 (CH), 130.6 (C), 130.2 (CH), 129.2 (CH), 128.9 (CH), 127.8 (CH), 127.3 (CH), 126.4 (CH), 56.2 (C), 20.0 (CH_3); ν_{max}/cm^{-1} 3022 w, 1741 w, 1698 v str, 1599 w, 1586 w, 1563 w, 1250 m, 1093 m, 1047 m, 885 m, 794 m, 749 v str, 711 w, 667 w; HRMS (APCI) *m/z* calc. for $C_{18}H_{14}O_2Cl$: 297.0677 $[M+H]^+$; found: 297.0680.

Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.3 mg, 11.3 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.4 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-phenylcyclopentene-1,3-dione **183l** (18.6 mg, 0.100 mmol, 1 equiv.), was added to the solution followed by DMA (0.6 mL) and 3-chlorophenylboronic acid (33.8 mg, 0.24 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 27 h under an O_2 atmosphere (balloon) and with an air condensor. Additional portions of (*S*)-4-*tert*-Butyl-2-(2-pyridyl)oxazoline **210** (1.1 mg, 5.4 μmol, 0.05 equiv.) and $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.05 equiv.) were added and the reaction was left to stir for a further 68 h at 50 °C under an O_2 atmosphere. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (25:1 hexane:EtOAc,) to obtain 4-(3-chlorophenyl)-2-methyl-2-phenylcyclopent-4-ene-1,3-dione **201ll** (14.7 mg, 0.049 mmol, 49%) as a yellow oil (56:44 er).

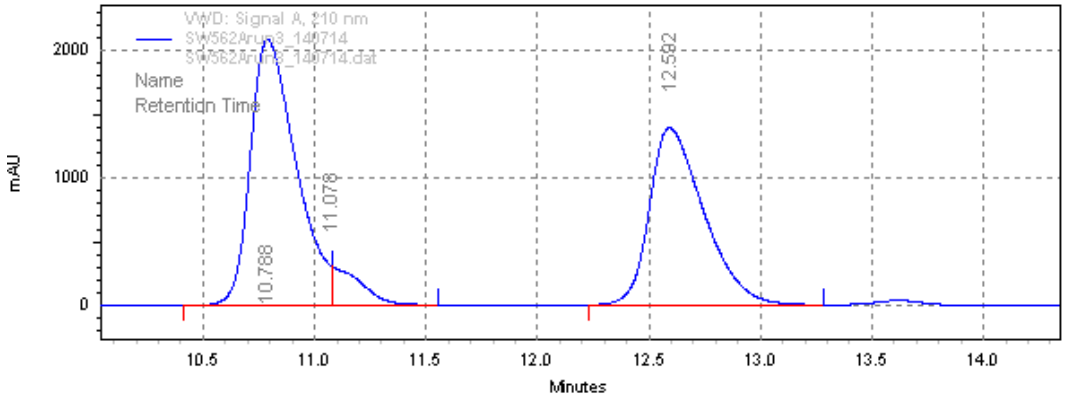
See racemic procedure above for characterisation.

$[\alpha]_D^{26}$ = +18.6 (*c* 0.22, $CHCl_3$); 56:44 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 210 nm) t_R of major isomer: 10.8 min, t_R of minor isomer: 12.6 min.



VWD: Signal A,
210 nm Results

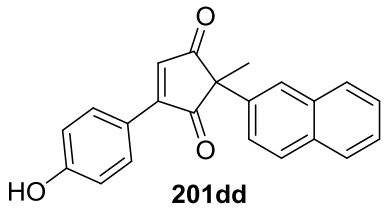
Retention Time	Area	Area %	Height	Height %
10.527	478708269	47.19	33490515	51.22
12.228	478535185	47.17	28080768	42.94
13.043	57226496	5.64	3819997	5.84



VWD: Signal A,
210 nm Results

Retention Time	Area	Area %	Height	Height %
10.788	497327986	53.07	34935336	55.21
11.078	45377672	4.84	5043107	7.97
12.592	394478253	42.09	23294299	36.82

4-(4-Hydroxyphenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione (201dd)



201dd

Racemic procedure:

4-Hydroxyphenyl boronic acid **6d** (30.7 mg, 0.223 mmol, 2.2 equiv.) was added to dried glassware and dehydrated to the boroxine under vacuum with a heat gun, then an N_2 atmosphere was introduced. 2-Methyl-2-(naphthalen-2-yl)cyclopentane-1,3-dione **183d** (23.7 mg, 0.100 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.2 mg, 6.6 μmol, 0.066 equiv.) and $Pd(OAc)_2$ (1.2 mg, 5.3 μmol, 0.053 equiv.) were added sequentially, with an N_2 environment being reintroduced after each addition. DMF (1 mL) was added and the reaction was left to stir at 70 °C under an O_2 atmosphere (balloon). After 20 h, additional portions of 1,10-phenanthroline **44** (1.2 mg, 6.6 μmol, 0.066 equiv.), $Pd(OAc)_2$ (1.2 mg, 5.3 μmol, 0.053 equiv.) and DMF (0.1 mL) were added and the reaction was left to stir for a further 48 h. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 15:1→2:1) to yield 4-(4-hydroxyphenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201dd** (28.3 mg, 0.086 mmol, 86%) as an orange solid.

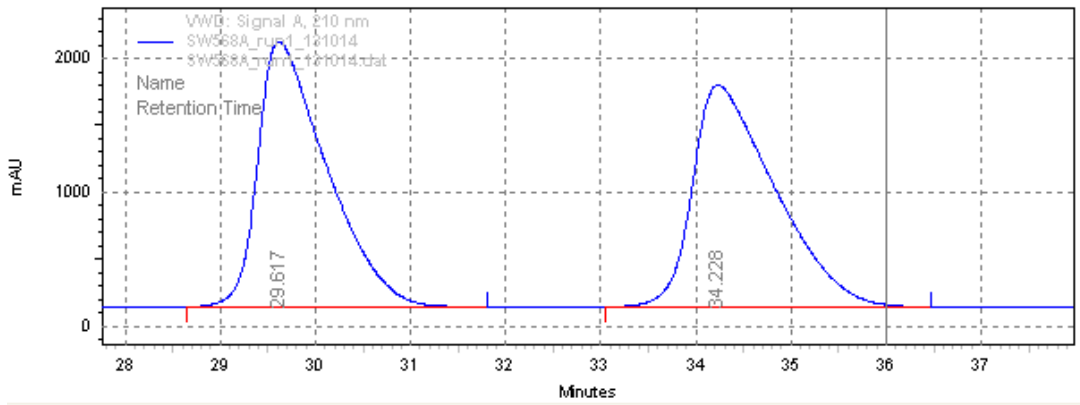
M.p. 159-161 °C; R_f = 0.26 (1:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.8 Hz, 2H, Ar-H), 7.83 – 7.75 (m, 4H, Ar-H), 7.53 – 7.42 (m, 3H, Ar-H), 7.37 (s, 1H, alkene-H), 6.89 (d, J = 8.8 Hz, 2H, Ar-H), 6.38 (s, 1H, O<u>H</u>), 1.76 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.6 (C), 203.9 (C), 159.4 (C), 155.8 (C), 137.8 (CH), 134.9 (C), 133.2 (C), 132.5 (C), 131.7 (CH), 128.7 (CH), 128.1 (CH), 127.5 (CH), 126.36 (CH), 126.34 (CH), 125.7 (CH), 124.1 (CH), 121.4 (C), 116.2 (CH), 56.4 (C), 19.8 (CH_3); ν_{max}/cm^{-1} 3380 br, 3052 w, 2984 w, 1733 w, 1683 v str, 1605 m, 1568 v str, 1580 v str, 1510 str, 1434 m, 1236 v str, 1179 v str, 1102 str, 840 str, 816 str, 743 str; HRMS (NSI) *m/z* calc. for $C_{22}H_{17}O_3$: 329.1172 $[M+H]^+$; found: 329.1175.

Enantioselective procedure:

(*S*)-4-(*Tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** (3.0 mg, 11.0 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.4 mL), followed by $Pd(OAc)_2$ (2.4 mg, 10.7 μmol, 0.11 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.7 mg, 0.1003 mmol, 1 equiv.), was added to the solution followed by DMA (0.6 mL) and 4-hydroxyphenyl boronic acid **6d** (29.2 mg, 0.244 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 10:1→2:1) to yield (*S*)-4-(4-hydroxyphenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201dd** (33.6 mg, 0.100 mmol, 100%) as a yellow solid (83:17 er).

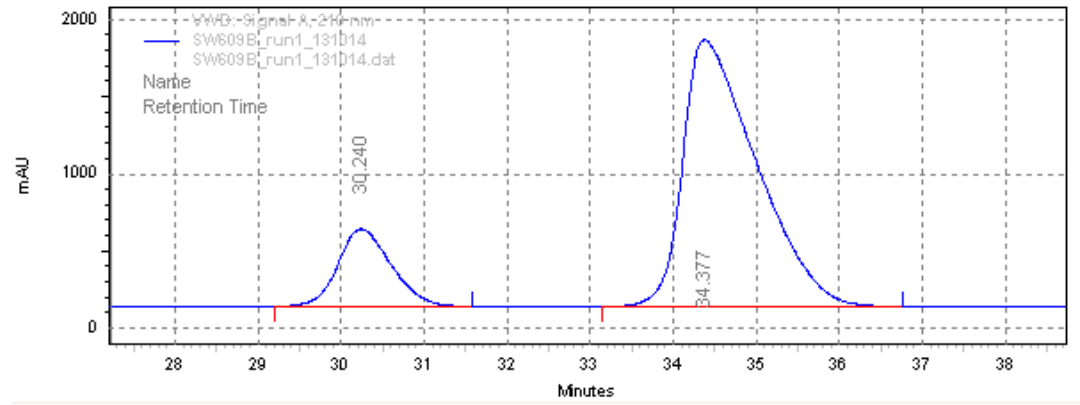
See racemic procedure above for characterisation.

$[\alpha]_D^{22}$ = +122.0 (*c* 1.00, $CHCl_3$); 83:17 er; HPLC (CHIRALPAK IA, hexane/2-propanol: 90/10, flow rate: 1.0 mL min^{-1}, detection UV 210 nm, 25 °C) t_R of major isomer: 34.4 min, t_R of minor isomer: 30.2 min.



VWD: Signal A, 210 nm Results

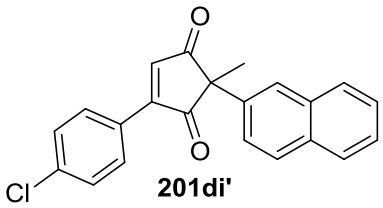
Retention Time	Area	Area %	Height	Height %
29.617	1676787643	50.00	33240353	54.46
34.228	1676497371	50.00	27794072	45.54



VWD: Signal A, 210 nm Results

Retention Time	Area	Area %	Height	Height %
30.240	375245307	17.34	8413332	22.49
34.377	1788967092	82.66	28987796	77.51

4-(4-Chlorophenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione (201di')



201di'

Racemic procedure:

4-Chlorophenyl boronic acid **6i'** (34.6 mg, 0.221 mmol, 2.2 equiv.) was heated (heat gun) under vacuum in the reaction flask to convert it to the boroxine before an N_2 environment was introduced. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.8 mg, 0.101 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.0 mg, 5.6 μmol, 0.06 equiv.) and $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.05 equiv.) were then added in order, with a N_2 environment being re-introduced after each addition. Anhydrous DMF (1 mL) was then added before the solution was stirred at 70 °C in an O_2 environment (balloon) for 72 h. On completion, diethyl ether and ethyl acetate were added to the reaction solution before being washed with water (10 mL) and brine (10 mL). The aqueous layer was washed with Et_2O (5 mL) and EtOAc (2.5 mL) until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried with $MgSO_4$ before solvent was removed under reduced pressure. The crude was purified by silica-gel column chromatography (hexane/ethyl acetate 50:1), to yield 4-(4-chlorophenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201di'** (27.7 mg, 0.0799 mmol, 79%) as a yellow solid.

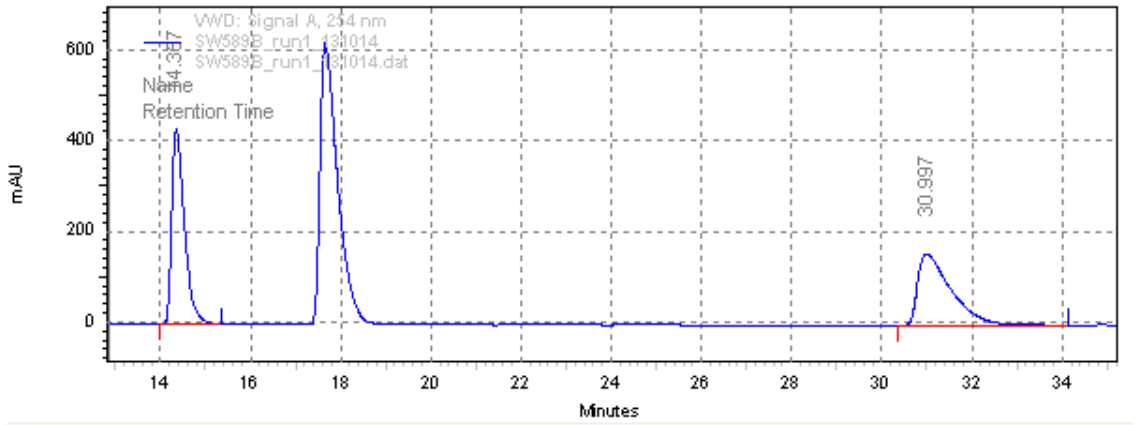
M. p. 130-135 °C; Yellow solid; R_f = 0.87 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.6 Hz, 2H, Ar-H), 7.86 – 7.73 (m, 4H, Ar-H), 7.56 – 7.39 (m, 6H, Ar-H and alkene-H), 1.75 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8 (C), 203.1 (C), 154.9 (C), 140.3 (CH), 138.2 (C), 134.6 (C), 133.2 (C), 132.5 (C), 130.6 (CH), 129.4 (CH), 128.8 (CH), 128.1 (CH), 127.5 (CH), 127.4 (C), 126.4 (CH × 2), 125.6 (CH), 124.0 (CH), 56.3 (C), 20.1 (CH_3); ν_{max}/cm^{-1} 3051 w, 1738 w, 1689 v str, 1589 str, 1558 w, 1484 m, 1314 m, 1244 str, 1092 v str, 1014 m, 826 str, 749 str; HRMS (APCI) *m/z* calc. for $C_{22}H_{16}O_2Cl$: 347.0833 $[M+H]^+$; found: 347.0830.

Enantioselective procedure:

(*S*)-4-(*Tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** (3.1 mg, 11.0 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.4 mL), followed by $Pd(OAc)_2$ (2.4 mg, 10.7 μmol, 0.11 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.7 mg, 0.1003 mmol, 1 equiv.), was added to the solution followed by DMA (0.6 mL) and 4-chlorophenyl boronic acid **6i'** (33.6 mg, 0.243 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 50:1) to yield (*S*)-4-(4-chlorophenyl)-2-methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201di'** (29.7 mg, 0.0856 mmol, 85%) as a yellow solid (94:6 er).

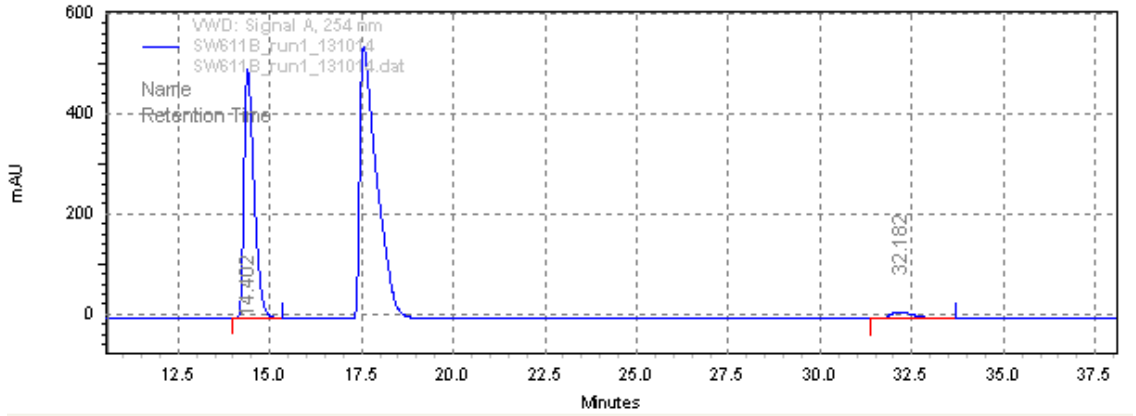
See racemic procedure for characterisation.

$[\alpha]_D^{23}$ = +56.8 (*c* 0.35, $CHCl_3$); 94:6 er; HPLC (CHIRALPAK IB, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 14.4 min, t_R of minor isomer: 32.2 min.



VWD: Signal A,
254 nm Results

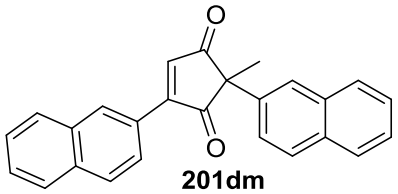
Retention Time	Area	Area %	Height	Height %
14.357	137807233	50.46	7240160	73.33
30.997	135267797	49.54	2633611	26.67



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
14.402	157246667	93.98	8325327	97.41
32.182	10068139	6.02	221416	2.59

2-Methyl-2,4-di(naphthalen-2-yl)cyclopent-4-ene-1,3-dione (201dm)



201dm

Racemic procedure:

2-Naphthalene boronic acid **6m** (38.2 mg, 0.222 mmol, 2.2 equiv.) was heated (heat gun) under vacuum in the reaction flask to convert it to the boroxine before an N_2 environment was introduced. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.5 mg, 0.995 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.0 mg, 5.6 μmol, 0.06 equiv.) and $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.05 equiv.) were then added in order, with a N_2 environment being re-introduced after each addition. Anhydrous DMF (1 mL) was then added before the solution was stirred at 70 °C in an O_2 environment (balloon) for 72 h. On completion, diethyl ether and ethyl acetate were added to the reaction solution before being washed with water (10 mL) and brine (10 mL). The aqueous layer was washed with Et_2O (5 mL) and EtOAc (2.5 mL) until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried with Na_2SO_4 before solvent was removed under reduced pressure. The crude was purified by silica-gel column chromatography (hexane/ethyl acetate 25:1→20:1), to yield 2-methyl-2,4-di(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201dm** (29.9 mg, 0.0825 mmol, 83%) as a yellow solid.

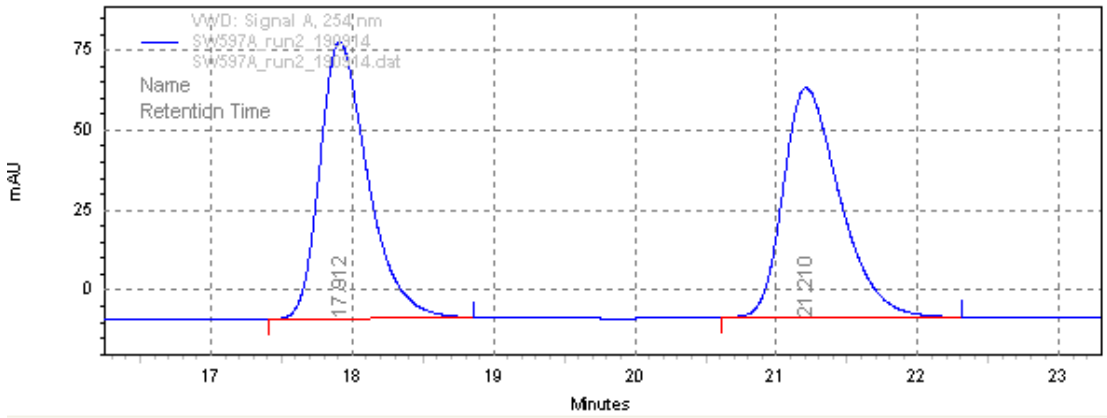
M. p. 160-162 °C; R_f = 0.80 (2:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 – 8.71 (m, 1H, Ar-H), 8.11 – 7.72 (m, 8H, Ar-H), 7.67 – 7.39 (m, 6H, Ar-H and alkene H), 1.81 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.3 (C), 203.3 (C), 155.8 (C), 140.2 (CH), 134.9 (C), 134.6 (C), 133.2 (C), 132.9 (C), 132.5 (C), 131.1 (CH), 129.5 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 126.4 (CH), 126.3 (CH), 126.2 (C), 125.7 (CH), 124.9 (CH), 124.1 (CH), 56.5 (C), 20.1 (CH_3); ν_{max}/cm^{-1} 3053 w, 1736 w, 1689 v str, 1600 w, 1565 w, 1581 w, 1263 m, 898 m, 863 m, 813 m, 741 v str; HRMS (APCI) *m/z* calc. for $C_{26}H_{19}O_2$: 363.1380 $[M+H]^+$; found: 363.1380.

Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.3 mg, 11.3 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.8 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.8 mg, 0.1007 mmol, 1 equiv.), was added to the solution followed by DMA (0.2 mL) and 2-Naphthalene boronic acid **6m** (37.6 mg, 0.244 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 20:1) to yield (*S*)-2-methyl-2,4-di(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **201dm** (33.6 mg, 0.093 mmol, 92%) as a yellow solid (74:26 er).

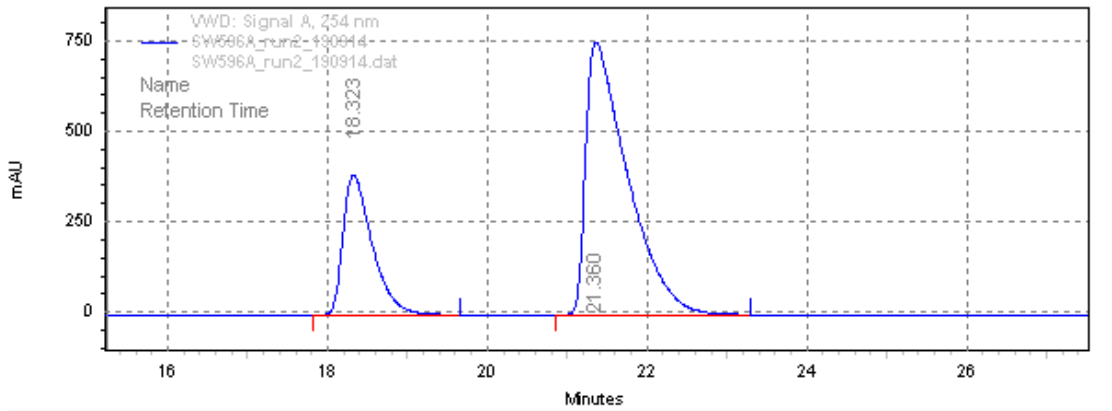
See racemic procedure for characterisation.

$[\alpha]_D^{23}$ = +184.0 (*c* 1.00, $CHCl_3$); 74:26 er; HPLC (CHIRALPAK IB, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 21.4 min, t_R of minor isomer: 18.3 min.



VWD: Signal A,
254 nm Results

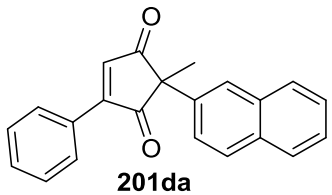
Retention Time	Area	Area %	Height	Height %
17.912	34143414	50.56	1451936	54.73
21.210	33385414	49.44	1201031	45.27



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
18.323	164900728	26.37	6500329	33.96
21.360	460398841	73.63	12638868	66.04

2-Methyl-2-(naphthalen-2-yl)-4-phenylcyclopent-4-ene-1,3-dione (201da)



201da

Racemic procedure:

Phenyl boronic acid **6a** (27.0 mg, 0.222 mmol, 2.2 equiv.) was heated (heat gun) under vacuum in the reaction flask to convert it to the boroxine before an N_2 environment was introduced. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.9 mg, 0.101 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.0 mg, 5.6 μmol, 0.05 equiv.) and $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.05 equiv.) were then added in order, with a N_2 environment being re-introduced after each addition. Anhydrous DMF (1 mL) was then added before the solution was stirred at 70 °C in an O_2 environment (balloon) for 72 h. On completion, diethyl ether and ethyl acetate were added to the reaction solution before being washed with water (10 mL) and brine (10 mL). The aqueous layer was washed with Et_2O (5 mL) and EtOAc (2.5 mL) until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried with Na_2SO_4 before solvent was removed under reduced pressure. The crude was purified by silica-gel column chromatography (hexane/ethyl acetate 20:1), to yield 2-methyl-2-(naphthalen-2-yl)-4-phenylcyclopent-4-ene-1,3-dione **201da** (26.4 mg, 0.0845 mmol, 84%) as a yellow solid.

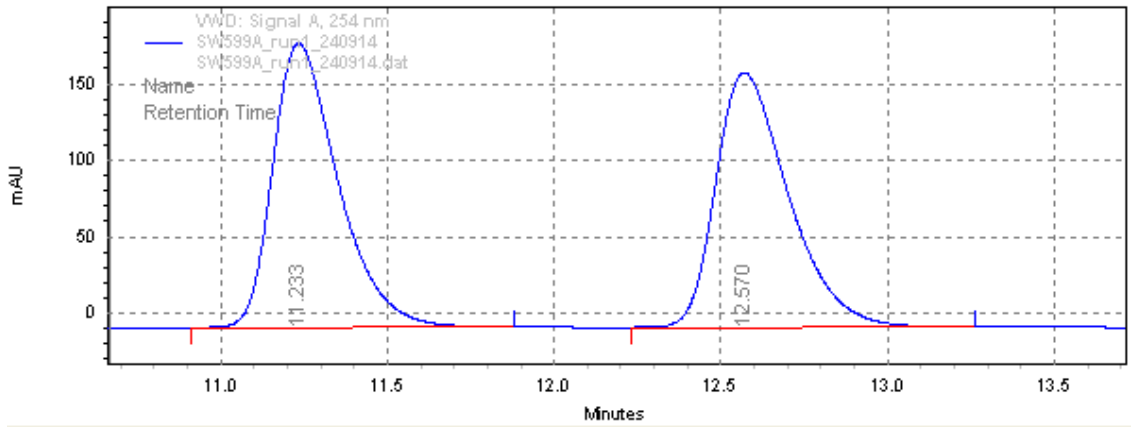
M. p. 108-110 °C; R_f = 0.74 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 – 7.94 (m, 2H, Ar-H), 7.89 – 7.73 (m, 4H, Ar-H), 7.59 – 7.40 (m, 7H, Ar-H and alkene-H), 1.76 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.0 (C), 203.4 (C), 156.3 (C), 140.4 (CH), 134.8 (C), 133.2 (C), 132.5 (C), 131.8 (CH), 129.4 (CH), 129.01 (CH), 128.97 (C), 128.7 (CH), 128.1 (CH), 127.5 (CH), 126.4 (CH × 2), 125.7 (CH), 124.1 (CH), 56.3 (C), 20.0 (CH_3); ν_{max}/cm^{-1} 3054 w, 1737 w, 1691 v str, 1596 m, 1506 m, 1446 m, 1246 str, 1104 m, 1050 m, 922 str, 808 str, 762 str; HRMS (NSI) *m/z* calc. for $C_{22}H_{17}O_2$: 313.1223 $[M+H]^+$; found: 313.1227.

Enantioselective procedure:

(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (2.4 mg, 11.8 μmol, 0.12 equiv.) was added to a dried flask, purged with N_2. DMA (0.8 mL), followed by $Pd(OAc)_2$ (2.3 mg, 10.2 μmol, 0.10 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.6 mg, 0.0999 mmol, 1 equiv.), was added to the solution followed by DMA (0.2 mL) and phenyl boronic acid **6a** (24.7 mg, 0.24 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was left to stir at 50 °C for 95 h under an O_2 atmosphere (balloon) and with an air condenser. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane / EtOAc, 20:1) to yield (*S*)-2-methyl-2-(naphthalen-2-yl)-4-phenylcyclopent-4-ene-1,3-dione **201da** (30.4 mg, 0.097 mmol, 97%) as a yellow solid (74:26 er).

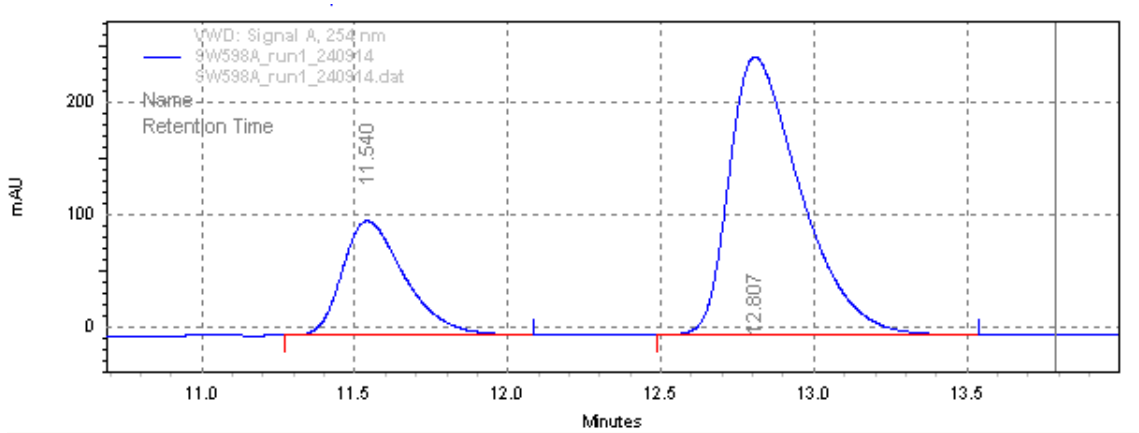
See racemic procedure for characterisation.

$[\alpha]_D^{23}$ = +74.0 (*c* 1.00, $CHCl_3$); 74:26 er; HPLC (CHIRALPAK IB, hexane/2-propanol: 99/1, flow rate: 1.0 mL min^{-1}, detection UV 254 nm, 25 °C) t_R of major isomer: 12.8 min, t_R of minor isomer: 11.5 min.



VWD: Signal A, 254 nm Results

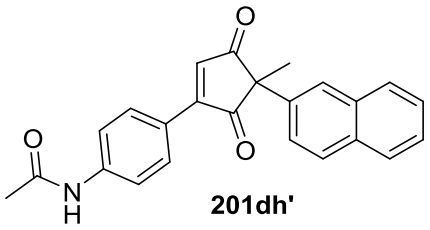
Retention Time	Area	Area %	Height	Height %
11.233	42444601	50.07	3114921	52.74
12.570	42333898	49.93	2791206	47.26



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
11.540	24260799	26.32	1714583	29.15
12.807	67904196	73.68	4167749	70.85

***N*-(4-(4-Methyl-4-(naphthalen-2-yl)-3,5-dioxocyclopent-1-en-1-yl)phenyl)acetamide (201dh')**



201dh'

Racemic procedure:

4-Acetamidophenylboronic acid **6h'** (39.5 mg, 0.221 mmol, 2.2 equiv.) was heated (heat gun) under vacuum in the reaction flask to convert it to the boroxine before an N_2 environment was introduced. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.6 mg, 0.999 mmol, 1 equiv.), 1,10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.3 mg, 5.8 μmol, 0.06 equiv.) were then added in order, with a N_2 environment being re-introduced after each addition. Anhydrous DMF (1 mL) was then added before the solution was stirred at 70 °C in an O_2 environment (balloon). After 24 h, further portions of 10-phenanthroline **44** (1.2 mg, 6.7 μmol, 0.07 equiv.) and $Pd(OAc)_2$ (1.3 mg, 5.8 μmol, 0.06 equiv.) were added and the reaction stirred for a further 24 h. On completion, diethyl ether and ethyl acetate were added to the reaction solution before being washed with water (10 mL) and brine (10 mL). The aqueous layer was washed with Et_2O (5 mL) and EtOAc (2.5 mL) until the organic layer was colourless. The combined organic layers were washed with brine (15 mL) and dried with Na_2SO_4 before solvent was removed under reduced pressure. The crude was purified by silica-gel column chromatography (hexane/ethyl acetate 1:1), to yield *N*-(4-(4-methyl-4-(naphthalen-2-yl)-3,5-dioxocyclopent-1-en-1-yl)phenyl)acetamide **201dh'** (31.5 mg, 0.0853 mmol, 85%) as a thick yellow oil.

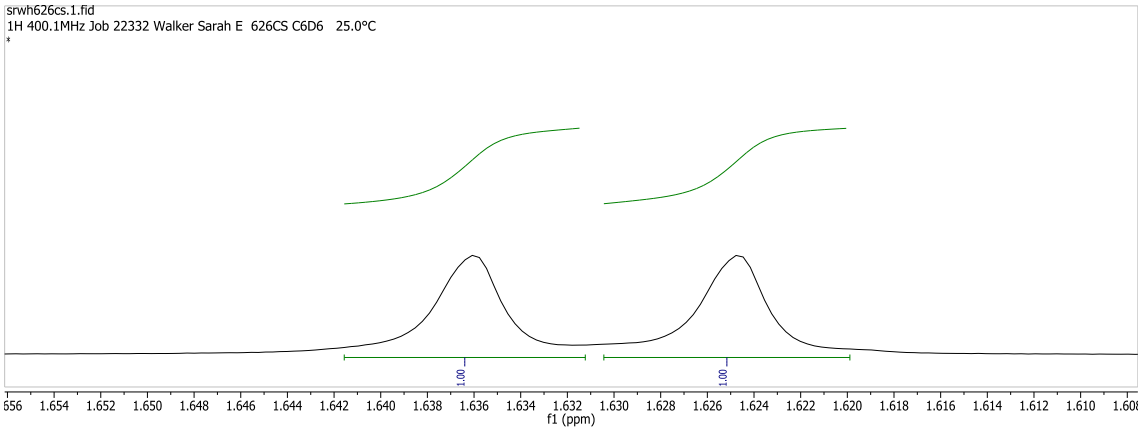
R_f = 0.29 (1:2 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.8 Hz, 2H, Ar-H), 7.89 – 7.71 (m, 5H, Ar-H and NH), 7.64 (d, J = 8.7 Hz, 2H, Ar-H), 7.53 – 7.37 (m, 4H, Ar-H and alkene H), 2.18 (s, 3H, CH_3), 1.74 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.3 (C), 203.3 (C), 168.4 (C), 155.2 (C), 141.2 (C), 139.0 (CH), 134.9 (C), 133.2 (C), 132.5 (C), 130.6 (CH), 128.7 (CH), 128.1 (CH), 127.5 (CH), 126.4 (CH), 126.3 (CH), 125.7 (CH), 124.5 (C), 124.1 (CH), 119.5 (CH), 56.3 (C), 24.8 (CH_3), 20.0 (CH_3); ν_{max}/cm^{-1} 3312 w, 2973 w, 1737 w, 1689 v str. 1590 str, 1507 v str, 1410 m, 1368 m, 1317 str, 1244 v str, 1183 m, 745 v str; HRMS (NSI) *m/z* calc. for $C_{24}H_{20}O_3N$: 370.1438 $[M+H]^+$; found: 370.1428.

Enantioselective procedure:

(*S*)-4-(*Tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** (3.0 mg, 11.0 μmol, 0.11 equiv.) was added to a dried flask, purged with N_2. DMA (0.5 mL), followed by $Pd(OAc)_2$ (2.4 mg, 10.7 μmol, 0.11 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-Methyl-2-(naphthalen-2-yl)cyclopent-4-ene-1,3-dione **183d** (23.8 mg, 0.1007 mmol, 1 equiv.), was added to the solution followed by DMA (0.5 mL) and 4-acetamidophenylboronic acid **6h'** (38.8 mg, 0.241 mmol, 2.4 equiv.) which was freshly dehydrated under vacuum with a heat gun to form the boroxine. The reaction was then left to stir at 50 °C under an O_2 atmosphere (balloon) and with an air condenser. After 48 h, additional portions of ligand **64** (3.0 mg, 11.0 μmol, 0.11 equiv.) and $Pd(OAc)_2$ (2.4 mg, 10.7 μmol, 0.11 equiv.) were added and the reaction left for a further 48 h. On completion, 2:1 EtOAc:Et_2O was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with 2:1 EtOAc:Et_2O until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc, 20:1) to yield (*S*)-*N*-(4-(4-methyl-4-(naphthalen-2-yl)-3,5-dioxocyclopent-1-en-1-yl)phenyl)acetamide **201dh'** (10.5 mg, 0.028 mmol, 28%) as a yellow solid (80:20 er).

See racemic procedure for characterisation.

$[\alpha]_D^{19}$ = +207.0 (*c* 0.155, $CHCl_3$); 80:20 er determined by high resolution ^1H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents (*R*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol.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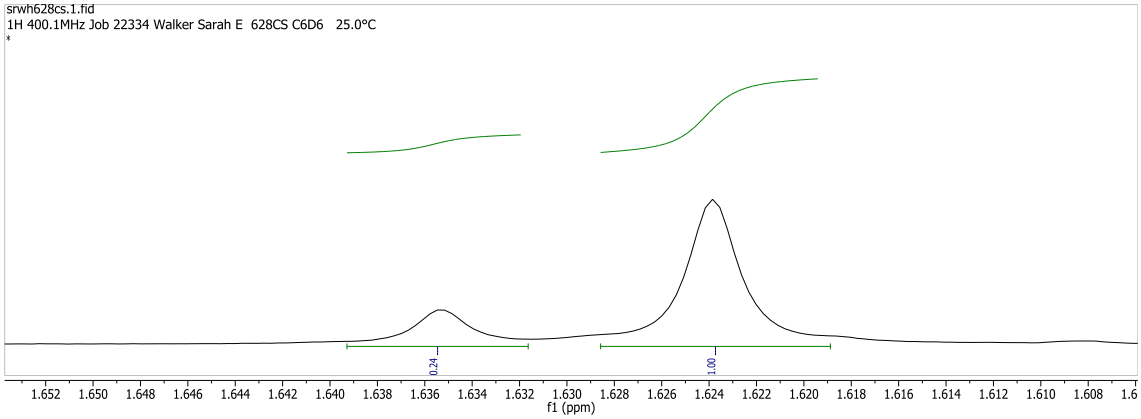
1H 400.1MHz Job 22332 Walker Sarah E 626CS C6D6 25.0°C
*
1.00
1.00
556 1.654 1.652 1.650 1.648 1.646 1.644 1.642 1.640 1.638 1.636 1.634 1.632 1.630 1.628 1.626 1.624 1.622 1.620 1.618 1.616 1.614 1.612 1.610 1.608
f1 (ppm)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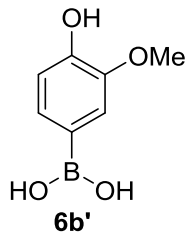
1H 400.1MHz Job 22334 Walker Sarah E 628CS C6D6 25.0°C
*
0.24
1.00
1.652 1.650 1.648 1.646 1.644 1.642 1.640 1.638 1.636 1.634 1.632 1.630 1.628 1.626 1.624 1.622 1.620 1.618 1.616 1.614 1.612 1.610 1.608 1.6
f1 (ppm)

Synthesis of Preussidone (189)

(4-Hydroxy-3-methoxyphenyl)boronic acid (6b')[37]

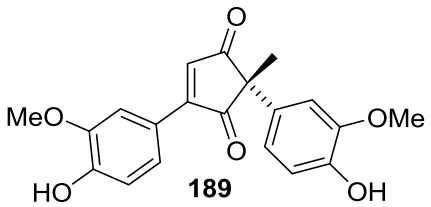


6b'

(4-Hydroxy-3-methoxyphenyl)boronic acid pinacol ester **215** (0.500 g, 2.00 mmol 1 equiv.), ammonium acetate (0.4627 g, 5.99 mmol, 3 equiv.) acetone (15 mL) and water (7 mL) were added to a flask. Once all reagents had dissolved, $NaIO_4$ (1.288 g, 6.00 mmol, 3 equiv.) was added and the reaction stirred for 18 h. The resulting reaction mixture was filtered, EtOAc (20 mL) and brine (20 mL) were added and the phases separated. The aqueous phase was washed with EtOAc (5 × 20 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ before solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1→1:1) followed by recrystallisation from acetone to yield (4-hydroxy-3-methoxyphenyl)boronic acid **6b'** (53.3 mg, 0.317 mmol, 16%) as a brown solid.

M.p. decomp. 210 °C; R_f = 0.43 (1:2 hexane/EtOAc); ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.68 (s, 1H, O<u>H</u>), 7.46 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.39 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar-H), 6.91 (s, 2H, O<u>H</u>), 6.81 (d, *J* = 7.8 Hz, 1H, Ar-H), 3.84 (s, 3H, CH_3); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 149.8 (C), 147.7 (C), 130.9 (C), 128.9 (CH), 117.9 (CH), 115.3 (CH), 56.1 (CH_3); ν_{max}/ cm^{-1} 3258 br str, 1595 str, 1518 str, 1458 w, 1417 str, 1336 v str, 1261 m, 1230 str, 1159 str, 1092 str, 1030 v str, 878 m, 819 m; HRMS (APCI) *m/z calc*. For $C_7H_9O_4{}^{10}B$: 167.0625; found: 167.0621.

2,4-Bis(4-hydroxy-3-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione (189)*



189

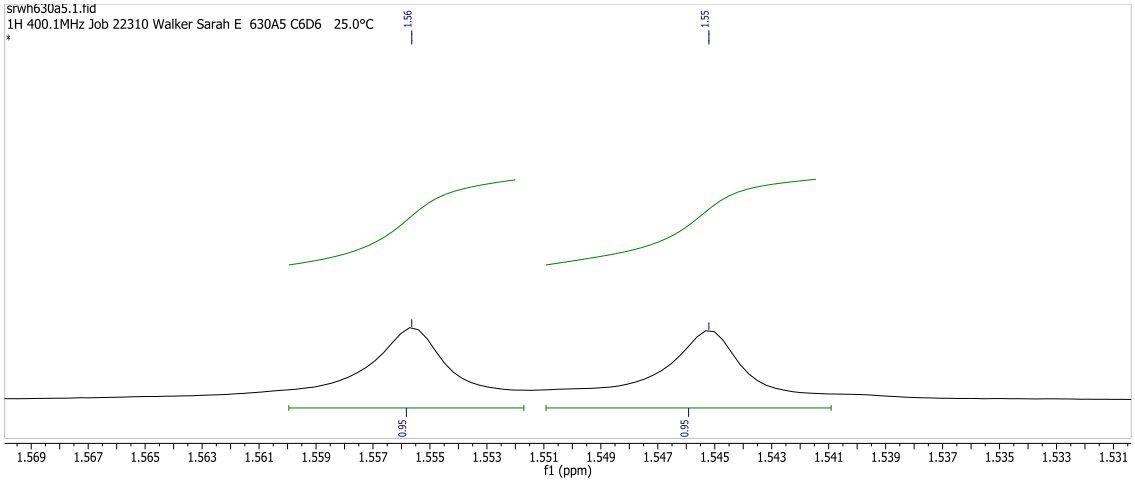
(*S*)-4-(*Tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** (1.5 mg, 5.5 μmol, 0.055 equiv.) was added to a dried flask, purged with N_2. DMA (0.5 mL), followed by $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.049 equiv.) were added and the solution was left to stir at room temperature for 1 h. 2-(4-Hydroxy-3-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione **183i** (23.2 mg, 0.0999 mmol, 1 equiv.), was added to the solution followed by DMA (0.5 mL) and 4-hydroxy-3-methoxyphenyl boronic acid pinacol ester **215** (62.5 mg, 0.250 mmol, 2.5 equiv.) and the reaction was left to stir at 50 °C under an O_2 atmosphere (balloon) and with an air condenser. Additional portions of both (*S*)-4-(*Tert*-Butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole **64** (1.5 mg, 5.5 μmol, 0.055 equiv.) and $Pd(OAc)_2$ (1.1 mg, 4.9 μmol, 0.049 equiv.) were added after 24 and 48 h. After a further 24 h, EtOAc was added to the reaction solution before being washed with H_2O and brine. The aqueous layer was extracted with EtOAc until the organic layer was colourless. The combined organic layers were washed with brine and dried over $MgSO_4$ and solvent was removed *via* reduced pressure. The resulting crude was purified by silica gel column chromatography (hexane/EtOAc 2:1) to yield 2,4-bis(4-hydroxy-3-methoxyphenyl)-2-methylcyclopent-4-ene-1,3-dione [(+)-preussidone)] **189** (28.1 mg, 0.0793 mmol, 79%) as a red oil (85:15 er).

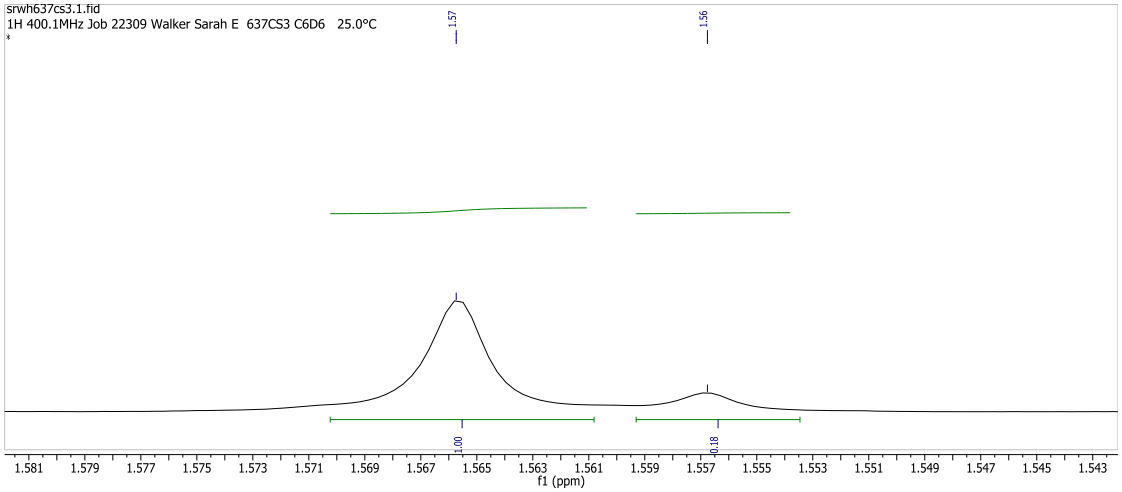
Red oil; R_f = 0.27 (2:1 EtOAc:hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 2.0 Hz, 1H, Ar-H), 7.59 (dd, J = 8.4, 2.0 Hz, 1H, Ar-H), 7.33 (s, 1H, alkene-H), 7.02 (d, J = 8.4 Hz, 1H, Ar-H), 6.90 (d, J = 2.0 Hz, 1H, Ar-H), 6.85 (d, J = 8.3 Hz, 1H, Ar-H), 6.80 (dd, J = 8.3, 2.0 Hz, 1H, Ar-H), 6.15 (s, 1H, O<u>H</u>), 5.65 (s, 1H, OH), 3.96 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 1.61 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.8 (C), 203.4 (C), 155.2 (C), 149.3 (C), 146.67 (C), 146.65 (C), 145.2 (C), 137.8 (CH), 129.5 (C), 124.1 (CH), 121.3 (C), 119.5 (CH), 115.1 (CH), 114.4 (CH), 111.6 (CH), 109.1 (CH), 56.1 (CH_3), 55.9 (CH_3), 55.7 (C), 20.2 (CH_3); 3411 br str, 2937 w, 1735 w, 1687 v str, 1573 m, 1508 v str, 1449 m, 1424 m, 1246 v str, 1204 v str, 1127 str, 1028 v

* ^{1}H and ^{13}C NMR spectra also obtained using acetone-d_6 as reference and data corresponds with literature data from Cichewicz and co-workers, *J. Nat. Prod.*, 2012, **75**, 1819-1823.

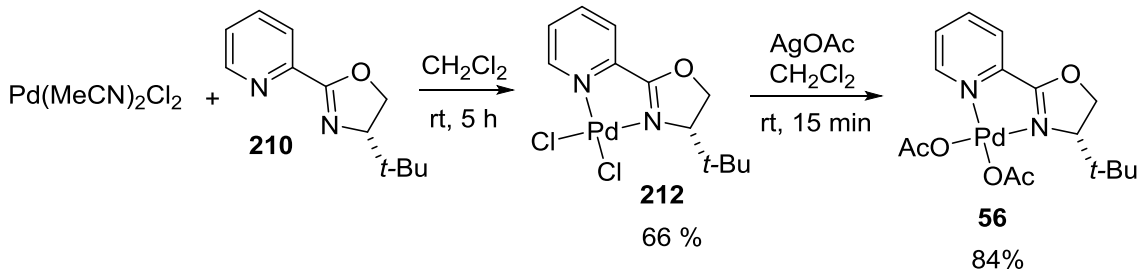
str, 908 str, 727 v str; HRMS (APCI) *m/z* calc. for $C_{20}H_{19}O_6$: 355.1176 $[M+H]^+$ found: 355.1181.

$[\alpha]_D^{20}$ = +78.0 (*c* 1.00, $CHCl_3$); 85:15 er determined by high resolution ^1H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 5.0 equivalents (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol.





Pd-pyridinyl-oxazoline acetate complex 56[34]



(*S*)-4-*Tert*-Butyl-2-(2-pyridyl)oxazoline **210** (25.1 mg, 0.123 mmo, 1.0 equiv.), $Pd(MeCN)_2Cl_2$ (31.8 mg, 0.123 mmol, 1.0 equiv.) and dichloromethane (1 mL) were stirred for 5 hours under an argon atmosphere at room temperature and with the exclusion of light. The mixture was then filtered through celite and concentrated to 0.1 mL *in vacuo.* The crude substrate was precipitated with hexane and the solid filtered and washed with Et_2O to yield **212** (31.0 mg, 0.0813 mmol, 66%, orange solid).

To a suspension of **212** (31.0 mg, 0.0813 mmol, 1 equiv.) in dichloromethane (2 mL), silver acetate (27.1 mg, 0.162 mmol, 2 equiv.) was added and the solution stirred in the absence of light for 15 min at room temperature. The suspension was then filtered and the filtrate was evaporated to dryness *in vacuo* to afford **56** as a orange solid (29.1 mg, 0.0679 mmol, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (s, 1H, Ar-H), 8.12 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.80 – 7.54 (m, 2H, Ar-H), 4.82 (dd, *J* = 9.3, 3.9 Hz, 1H, CH<u>H</u>), 4.74 (t, *J* = 9.3 Hz, 1H, C<u>H</u>H), 4.10 (dd, *J* = 9.3, 3.9 Hz, 1H, C<u>H</u>*t*-Bu), 2.10 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.01 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.4 (C), 178.3 (C), 168.5 (C), 151.1 (CH), 144.3 (C), 140.1 (CH), 129.0 (CH), 124.7 (CH), 74.1 (CH_2), 72.5 (CH), 34.7 (C), 25.8 (CH_3), 23.0 (CH_3); HRMS (NSI) *m/z calc*. for $C_{14}H_{19}O_3N_2{}^{102}Pd$: 365.0446 $[M\text{-}OAc]^+$; found: 365.0451.

4.9 References

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Appendix: Publications

1) S. E. Walker, J. Boehnke, P. E. Glen, S. Levey, L. Patrick, J. A. Jordan-Hore, A.-L. Lee, *Org. Lett.*, 2013, **15**, 1886-1889.
2) S. E. Walker, J. A. Jordan-Hore, D. G. Johnson, S. A. Macgregor, A.-L. Lee, *Angew. Chem. Int. Ed.*, 2014, **53**, 13876-13879.
3) S. E. Walker, C. J. C. Lamb, N. A. Beattie, P. Nikodemiak, A.-L. Lee, *Chem. Commun.*, 2015, **51**, 4089-4092.